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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

APRIL, 1931

ORIGINAL ARTICLES.

COD-LIVER OIL AND THE VITAMINS IN RELATION TO BONE GROWTH AND RICKETS.*†

By H. A. Harris, D.Sc., M.B., B.S.,

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"We *learn* from our masters—but we *see* with our own eyes."

Recent leading articles in the *British Medical Journal* have contained many references to discoveries of new functions of the vitamins; but no adequate retraction, if any, has been made of the claims concerning the functions erroneously ascribed to them. For several years Professors Mellanby and Drummond, the importance of whose contributions to the subject is a matter of common knowledge, were using the qualifying term "growth-promoting" in relation to fat-soluble vitamin A. Professor Mellanby[1] has now shifted his ground, and ascribes to fat-soluble vitamin A the function of protection of the organism from infection. Hence one is justified in asking what is to become of the claim that it is "growth-promoting." This question directly affects my attitude. From 1926 onward[2] I have questioned repeatedly on clinical and experimental grounds, the properties that have too hastily been ascribed to the elusive vitamins. The facts upon which I have laid particular emphasis are: (1) That the growth-promoting vitamins are water-soluble, and (2) that fat-soluble vitamin A was respon-

* Awarded the Alvarenga Prize of the College of Physicians of Philadelphia, 1930.

† My thanks are due to the Medical Research Council for a grant in aid of expenses, to Prof. Elliot Smith, F.R.S., and Prof. T. R. Elliott, F.R.S., for active interest, and to my colleagues Miss Audrey E. Russell, M.B., B.S., and Mr. F. Melville for continuous and painstaking assistance.

sible for differentiation of the tissues for special functions. For this, among many reasons, I propose to consider the history of cod-liver oil in therapeutics, as it affords a singularly clear example of the manner in which the empirical common sense of the layman has triumphed over the alternating scepticism and hasty speculations of the scientist and, in particular of the biochemist, in medicine. It is instructive to note that what one generation regards as obvious and beyond discussion in regard to issues on the borderline between clinical medicine and the laboratory, by a closely succeeding time may be confidently regarded as the opposite. The analyses of test meals, the urea-concentration test, blood urea, diastase reaction, opsonic index—all have their day. The present fashion in the cult of the vitamin is no exception. If scientific medicine is to be more than "the doubtful recording of successive events," it must enable us to understand the clinical applications of the discoveries in the laboratory. One speaks vaguely of "the lessons of the past," but the real lesson that we can learn from the past is to trace back our ideas, beliefs and tendencies to their origins in the hope of estimating them, and in particular their modern applications, at their true value. With this purpose in view I propose to summarize the history of the therapeutic uses of cod-liver oil with special reference to rickets, the misplaced optimism in regard to vitamin-therapy and the present state of our knowledge of the chemistry of bone.

A. Cod-liver Oil. The use of cod-liver oil as a prophylactic and curative agent owes nothing to the medical profession, but little to the biochemist, and only a modicum to the pharmacist. Cod-liver oil has been used as a household remedy by the fishing folk of the Atlantic seaboard for countless years; for, in the days before cows were kept in milk during the winter, cod-liver oil was one of the winter substitutes for milk and butter. It is barely more than a hundred years since the introduction of the "Dutch" system of root and clover feeding allowed cows to be kept in milk through the year.

The first record in medical literature of the use of cod-liver oil in England hails from Manchester, where Dr. Darbey prescribed it for rheumatism in the second half of the eighteenth century. The oil appeared in the British Pharmacopœia in 1771. In 1822 the Society of Arts of Utrecht offered a prize for the best essay on the chemical and therapeutic properties of cod-liver oil. The remedial properties of the oil in cases of rickets had enjoyed a wide reputation among the laity before medical men recognized its value. Schutte, in 1824, published the first definite series of cases to illustrate the curative action of the oil in rickets, and he stated that the healing could be produced in five to nine weeks. He gives credit for the recognition of the curative properties of the oil to Dr. Percival,[3] who was editor of the British Pharmacopœia in 1771.

In his treatise on the "Oleum Jecoris Aselli" Bennet,[4] probably the greatest of Scotch clinicians, in 1841 extolled the virtues of the oil in the treatment of certain forms of gout, rheumatism and tuberculosis. Bennet published a remarkable clinical report by Steinhaeuser, of Heidelberg (1840), on the action of the oil in rickets. This document deserves to be rescued as a classic in the history of therapeutics. It surpasses in vividness any of those picturesque advertisements which the more cautious among us daily consign to the waste-paper basket. He writes: "At first there appears to be a greater degree of activity in the nutritive functions. The appetite becomes more natural; the excretions per alvum more regular; the swollen and distended abdomen flatter and more soft; the dirty white color of the integuments and general scrofulous appearance disappear; the soft parts generally receive more turgor vitalis, the muscles more tone and the swollen glands, should any exist, gradually return to their normal size. Concerning its favorable action on the bones, I have remarked, that after taking the oil for some weeks (but sooner or later according to the degree of the disease), the swollen, protuberant epiphyses of the bones, especially those of the radius and ulna, become thinner, and, together with the osseous substance generally, more compact. The curvature occasioned in the softened bones, by the weight of the body and muscular action, as for instance in the extremities and vertebral column, gradually disappears of itself, if it has not already reached a high degree. The one-sided flattening of the thorax recovers its rounded form, and the angular prominent sternum again becomes flat. The prominence of the forehead disappears, the fontanelles close, and the head loses its large, misshaped and angular appearance. The development of the teeth proceeds with ease and in a more perfect manner, and every part of the child's frame exhibits a greater degree of activity. The children no longer sit silent, apathetic and unmovable, but their attention is attracted to what passes around them, and they seek to get up and move, or regain the power of locomotion, should they have previously possessed it."

By the middle of the nineteenth century such discerning clinicians as Trousseau and Bretonneau had done something to convince opposing physicians of the value of cod-liver oil in rickets. But, as in the case of quinin in malaria, of mercury and iodids in syphilis, the weight of the profession was put in the scale against the empirical knowledge of the layman. Even as late as 1912, the doyen of the pediatricians, the senior physician[5] at Great Ormond Street Hospital for Children, in the well-known textbook states: "There seems to be no specific virtue in cod-liver oil; any other oil will do equally well."

The empirical therapeutics of the layman may often be a fit subject for derision rather than for kindly sympathy. Yet Syden-

ham said: "Wise men know this—whatever is useful is good." In the Medical Research Council Report on Experimental Rickets (1921) Edward Mellanby says that "Probably the most common cause of rickets in children is a relatively deficient antirachitic vitamin and excessive bread." In 1841 John Hughes Bennet stated that in the treatment of various conditions by cod-liver oil "all substances abounding in starch are to be avoided."

The anemia of rickets has recently occupied a prominent place in experimental studies. Woenckhaus[6] and others maintain that rachitic rats consistently show erythropenia and leukopenia to such an extent that the blood changes may be regarded as a sensitive indicator of the presence of rickets. On the other hand, as regards the therapeutic treatment of rickets in rats, opinion is sharply divided. Jones[7] has maintained that the admixture of increasing amounts of ferrous sulphate to the diet leads to an oxidative destruction of the vitamins. Hart, Steenbock[8] and their coworkers maintain that the addition of pure inorganic iron (ferric chlorid) to a plain milk diet is unable to prevent the development of anemia in rats, but that the addition of a minute trace of copper to the iron prevents the anemia. Further confirmation of these experiments is awaited. It is of interest to note that Bennet, in addition to restricting food abounding in starch, stated that in rickets "a course of chalybeate waters has been found useful," for rachitic children frequently display an anemia.

The enthusiastic protagonist of modern medicine may be tempted to think that the clinical acumen of Bennet was little more than an unstable empiricism. It might also be imagined that qualifications for passing judgment in the matters under discussion were limited by the fact that many of the diseases now ascribed to a deficiency of vitamins (such as xerophthalmia) were unknown to him. But Bennet did not neglect these issues. He quotes von Ammon as follows: "If there was a tendency to rachitis the general constitution, as well as the state of the eyes, improved under the use of the oil." Cases of scrofulous ophthalmia, specks and ulcers of the cornea, chronic keratitis, xerosis or atrophy of the conjunctiva and cornea are described in turn by Bennet, who recognized that all yielded to intensive treatment by cod-liver oil.

In 1921 the Accessory Food Factors Committee (appointed jointly by the Lister Institute and the Medical Research Council) reported[9] that: "Xerophthalmia is considered a rare disease. Only among the negro slaves of Brazil and among the poorest and most ignorant inhabitants of Russia is it said to have been observed to any extent." The disease was known to Bennet and was treated effectively by cod-liver oil. Bloch,[9] of Copenhagen, has published detailed reports of cases in Danish children during the first three years of the World War, and has shown that cod-liver oil was a specific cure for the disease. Bloch stresses that the disease is

unknown in Norway and Sweden, and ascribes its prevalence in Denmark to the exclusive consumption of margarine as virtually the whole of the butter is exported. Furthermore, when as a result of the German U-boat blockade in February, 1917, no raw products for the manufacture of margarine could be imported into Denmark, butter was rationed and sold at a low price so that each child had 250 gm. a week. From that date everyone ate butter instead of margarine, and xerophthalmia disappeared in Denmark. This is a most convincing experiment on the value of a ration of butter to the population, and is much more conclusive than the incomplete experiments of the "Drink More Milk" campaign of the Empire Marketing Board, described in a recent number of the *British Medical Journal*.

The empirical therapeutics of Bennet are a remarkable tribute to his clinical ability. Unfortunately, when the physician does not know why a drug is effective, he readily ceases to believe that it is effective. On the other hand, if he can invent a satisfying (as distinct from a satisfactory) reason for the action of a drug, he continues to believe that it does act. These frailties of human judgment account not only for the neglect of cod-liver oil by the physician but for his continued belief in glycerophosphates and a host of other drugs which probably have no therapeutic action. The physician is not exempt from the innate tendencies of human nature: He, like all men, is still prone to self-exculpation, especially when accused of error. Furthermore, the clinical records of Bennet remind us of our inexhaustible capacity for appropriating what others have done for us with no thought of a "thank you," and also how rarely we consider the mental process by which we gain our clinical convictions. The psychology of conversion in matters therapeutic is even more elusive than that displayed in other departments of the advancement of natural knowledge.

B. **The Medley of the Vitamins.** For several years after the fundamental definition of accessory food factors (Hopkins) or vitamins (Funk), the problem appeared to be resolved in terms of three substances, vitamins A, B and C. Vitamin A was held to be the fat-soluble substance, deprivation of which led to rickets and xerophthalmia. For several years it was regarded as the "growth-promoting" vitamin, notwithstanding the well-known clinical fact that rickets develops only in the rapidly growing child. The connotation "growth-promoting" was singularly inappropriate, as one of the essential conditions for the production of rickets is growth, and the nongrowing animal cannot acquire rickets.

No sooner had the harassed practitioner and medical student learned a simple mnemonic for the results of deficiency of vitamins A, B and C, than vitamin A was shown by McCollum, following the suggestive work of Hopkins and Mellanby, to consist of a fat-soluble portion, vitamin A proper, unstable to heat and oxygen,

deficiency of which leads to xerophthalmia, and another fat-soluble portion called vitamin D (first called vitamin X) which was called the "antirachitic" vitamin. Vitamin D was shown to be more stable than vitamin A to both heat and oxidation. The separation of vitamin A and vitamin D was a distinct step forward. Yet most biochemists persisted in referring to the fat-soluble vitamin A as the "growth-promoting" vitamin as distinct from vitamin D, the "antirachitic" vitamin. The clinical fact that the nongrowing infant does not acquire rickets was still ignored. Even the report for 1926–1927 of the Medical Research Council, published in 1928, contains the statement that "means have been progressively devised for distinguishing between vitamin A, the absence of which *produces stunting of growth* and some characteristic eye changes, and vitamin D, the absence of which causes rickets." Vitamin A is, however, more cautiously referred to as "a" growth factor rather that "the" growth factor. But few of the workers (McCollum in particular is an exception) have seen fit to refer to vitamin A as the "antixerophthalmic" vitamin.

It was at this period (1924) that in America and Great Britain numerous attempts were made to produce concentrates or extracts of "growth-promoting" vitamin A and of "antirachitic" vitamin D. Commercialism of a most dangerous type appeared. Several men who were lacking in any personal experience of the human problems involved in the practice of medicine patented various methods for obtaining particularly potent extracts of cod-liver oil, the activities of which were grossly exaggerated. To Mellanby in particular belongs the credit for persistently adhering to the virtues of cod-liver oil in clinical practice as the simplest, cheapest and most effective prophylactic and curative treatment for rickets. This is neither the time nor the place to survey critically the abuses of the rapid discoveries in the field of the vitamins. Happily, scientific falsifiers are rare. On the other hand, certain commercial houses are interested primarily in the organization, growth and diffusion of their wares, and it is difficult to contradict their vaunted scientific aspirations. As Latham observed: "In our profession Science now jostles Practice as Quackery did formerly."

In 1922, at a time when the functions and properties of the "antirachitic" vitamin D had not been differentiated from the "growth-promoting" fat-soluble vitamin A proper, Drummond, Zilva and Coward[10] claimed that "the ultimate origin of the vitamin A found in the oils derived from fish, and particularly the fish-liver oils, *would appear* to be chiefly the unicellular marine plants." Continuing the argument they say: "The extraordinary rise in the number of marine plants which begins as soon as the intensity and duration of sunlight increases early in the year, is followed by a rapid rise in the organisms, largely copepods, and larval decapods and molluscs, whose growth and development are

dependent on their food supply *which consists of minute plants.* These minute animals, which forms a large proportion of plankton, contain relatively large quantities of vitamin A, *presumably derived* from the diatoms on which they have thriven. . . . The origin of the vitamin A in fish-liver oils has, *therefore,* been traced back to the synthetic powers of the marine algæ which forms the fundamental food supply of all marine animals."

In this facile manner was the conception of vegetable chlorophyll ingenuously woven into the fiber of the hemoglobin-containing fish, to the joy of the vegetarians. It was suggested that sunshine and bottled sunshine harnessed in the chlorophyll or other pigments in the marine algæ passed into molluscs and copepods, and so arrived at cod-liver oil. This hypothetical cycle of events was suggested and accepted without any attempt to ascertain whether the molluscs and copepods did in fact lead a vegetarian existence. In 1923 one of the keenest investigators of the Marine Biologic Association, Dr. Marie Lebour,[11] published a valuable account of "The Food of Plankton," and found that the animal organisms of the plankton *were not exclusively vegetarian* in their diet. The organisms included in the term plankton are extremely voracious, and prey on one another and on newly hatched and very young fishes. Lebour figures medusæ eating larval herring and sprat much larger than themselves. (Fig. 1.) Hence the plankton organisms are not exclusively vegetarian, but are markedly carnivorous. There is, in fact, little doubt that spawn and young fish form part of the natural food of the common Cœlenterates and pelagic worms.

When fish are not actively cannibalistic as regards their own species they eat other species. If they eat invertebrate organisms of the plankton they tend to eat those which in their turn have eaten ova and newly hatched fish. Thus, the cycle of vitamin A is not exclusively a direct vegetarian cycle from the sun to the marine plants and the plankton, but is a carnivorous cycle in that the older fish eat the organisms which have eaten the young fish. Steffanson was able to support himself in the Arctic on a purely carnivorous diet of seal, bear, fox and fish without suffering any dietary deficiency. No vegetarian enthusiast could support himself on an exclusively vegetarian diet in such a climate. It is evident, therefore, that the cycle of vitamin A in the animal world is much more concentrated than any cycle of vitamin A from the vegetable to the animal world. The various carnivorous animals and in particular the nocturnal ones, show no deficiency of vitamin A in the wild condition, because they eat the animal, such as the herbivorous, who has been put to the trouble of concentrating both vitamin A and D from the vegetable food. Even the herbivorous animals during the period of most active growth are not strictly herbivorous, but carnivorous, since they live and grow on mother's

milk. The hedgehog hunts from sundown to sunrise and cares nought for ultraviolet radiations, but he sees to it that he consumes the small animals and insects that have had their fair share of ultraviolet radiation during the day. From China to Peru, from Greenland to Syria, from Kashmir to Great Britain rickets displays

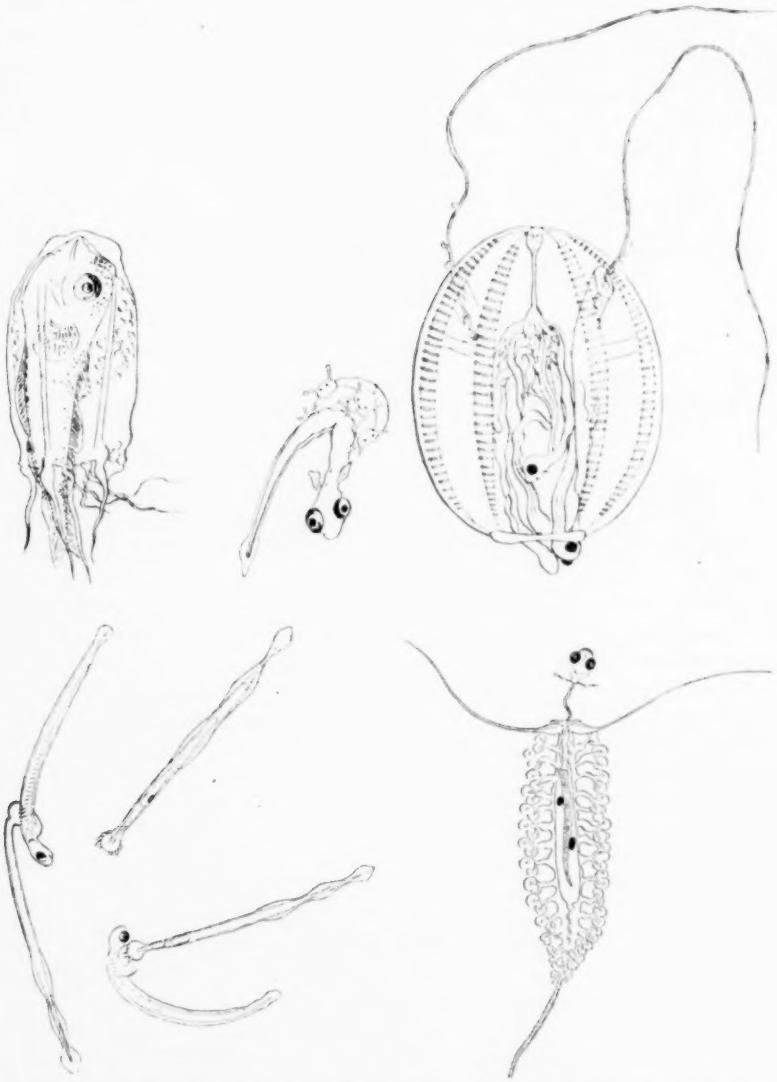

FIG. 1.—Various invertebrates of the plankton eating the young of invertebrates (such as herring and angler fish). (Reproduced from the Journal of the Marine Biological Association by kind permission of the Director Dr. E. J. Allen, F.R.S.)

its wide distribution. Exposure to sunshine is not necessarily the only or the most important element involved in its prevention.

C. **Sun Worship and Vitamin D.** The story of the preparation of the "antirachitic" vitamin D by the irradiation of ergosterol has been described with brilliant lucidity by Sir Walter Fletcher in the Report of the Medical Research Council for 1926–1927. Ultraviolet light, as shown by Rosenheim and Webster, in England, and Windhaus and Hess (of New York), in Germany, forms vitamin D in cholesterol and in ergosterol, a sterol which is obtained easily from ergot, various fungi and from yeast in particular. This highly important discovery has brought in its train an orgy of quackery. Hence it is imperative that steps should be taken to regain a sound clinical perspective. The craze for ultraviolet lamps, ultraviolet window glass and vitamin D as an addition to the various articles of diet is full of danger both to the community and to sound thinking. A *balanced diet of good fresh animal and vegetable food requires no addition of synthetic vitamins, as good wine needs no bush.* The addition of synthetic vitamins to the diet may be justifiable only as a temporary palliative in the case of those who are too poor to buy fresh food, of those who are too ignorant to know fresh food and of those who are too mean to pay the price of fresh food.

In the case of a branch of experimental medicine in which rapid progress is made by virtue of the sudden and varied accretions to preëxisting knowledge it is essential that old opinions should be revised or even rejected without any discredit to the previous observers. The acceptance of the soundness of the new experiments does not call for the rejection of all the old facts. It is not the main function of science to prove that an eminent man was mistaken. Much bad blood has been spilled in the attempt to distinguish between a contradictory meaning on the one hand and an irrational fact on the other. In considering some of the experimental results published by various observers in the light of justifiable scientific criticisms, a plea is put forward for the need of crucial experiments as a final reply to scientific doubt. The recent experiments of Mellanby in relation to the effect of vitamin D on dental caries has provoked an extended correspondence in the *British Medical Journal.* To her main contention, that vitamin D prevents caries, there is need of the counterproof that subsequent removal of vitamin D reproduces caries. This would be the *experimentum crucis* which would establish the relation of cause to effect in the difficult question of dental caries.

A few recent experiments may be considered as an index of the failure of most observers to reduce the experimental conditions to as definite and as simple as possible. Bacharach[12] recently published a series of experiments in which it was claimed that vitamin D was growth-promoting as well as antirachitic and that "the

growth-promoting properties of vitamin D can be directly illustrated by the use of suitable basal diets." The basal diet in these experiments *contained 5 per cent of a commercial yeast extract*, the most readily available source of active growth-promoting vitamins! Not only is yeast extract rich in growth-promoting vitamin B (the vitamin B_2 of Peters), but yeast extract in itself is the main source of manufacture of vitamin D today. The hypothetical growth-promoting properties of vitamin D cannot be tested for in the presence of vitamin B and vitamin D in the yeast of the basal diet.

The commercial laboratories are not alone in designing unsound experiments and publishing misleading results. Certain official organizations have been prone to sponsor unsound methods of assaying the elusive vitamins. The official Pharmacopœia of the United States, tenth edition, 1926, provides a vitamin A assay for cod-liver oil: "This assay is based upon the estimation of the minimum amount of cod-liver oil necessary to meet specific growth-promoting requirements in a standard test animal. The test animals shall be albino rats from a constant source and bred preferably under the control of the experimenter.

"The vitamin A potency of cod-liver oil shall be expressed in units per gram of oil, the unit to be the minimum daily amount of cod-liver oil required to cure induced symptoms of vitamin A starvation in young albino rats, and to cause a gain in weight of from 10 to 20 gm. within a period of thirty-five days under the conditions of growth and diet specified in this assay.

"Place on a vitamin-A-free diet rats not less than twenty-five days and not more than twenty-nine days old, and weighing not less than 35 gm. and not more than 45 gm.

"The basal diet is to be composed as follows:

Casein, or desiccated fresh meat rendered free from vitamin A	18 per cent
Salt mixture, such as that of Osborne and Mendel or McCollum and Davis	4 per cent
Starch, sufficient to make	100 per cent

"Use sufficient dried brewer's yeast to meet the vitamin B requirements of the animal, mixing it with the basal diet during the vitamin-A-free period.

"The rats shall begin receiving the cod-liver oil to be tested after not less than seven days of stationary or declining weight, and from the time of feeding the test oil, they shall be kept in separate cages.

"The test period shall continue for *thirty-five days*, and the potency of the oil shall be judged from the rat or rats showing a gain on the thirty-fifth day of between 10 and 20 gm. over the weight at the beginning of the test, and the cure of the induced symptoms of vitamin A starvation. Each test shall be controlled by at least two standard rats which have received no cod-liver oil. These

animals may serve as controls for any number of concurrent tests on which the same basal diet is used."

Every statement in this respect of the official test is misleading. The rat is not a living test-tube but a complex animal, the biologic processes of which are almost as complicated as those of man, with a susceptibility to intercurrent infections and illnesses, the influence from which must be considered together with the diet, however standardized the experimental conditions. To note one point on the biologic side, the rat of under thirty days is treated with the oil which is being tested for a period of thirty-five days. Translating this in terms of human rickets (the elucidation of which is the ultimate purpose of the research), it suggests that the rachitic babe of nine months should be treated with the oil for a year, whereas it is well known that the curative effects of cod-liver oil are displayed in human rickets in ten days. Further, the test is commenced when the weight of the rats is stationary or declining, whereas the rachitic babe attending the hospital clinic gains weight actively in the early stages of rickets. Lastly, the potency of the oil in the rats is judged by the *gain* of weight, whereas the efficiency of cod-liver oil in human rickets is often judged by the relative *loss* in weight.

The American Pharmacopœia is not alone in error. From the new laboratories of the Pharmaceutical Society of Great Britain have appeared several papers dealing with the "antirachitic" vitamin D. A summary of the recent research, complete with a sample of milk chocolate, has recently been distributed gratuitously to the medical profession. In this summary (dated 1928) it states: "The figures appear to indicate that milk contains vitamin D over and above that present in milk fat, and that the whole of this vitamin is retained in the chocolate. This suggests that milk chocolate prepared by our process would be found a useful adjuvant in *ultraviolet ray therapy*, and that since ———— milk chocolate and ———— milk chocolate contain all the calcium and phosphates present in the milk, these chocolates are preëminently the sweetmeats for growing children." And again: "The milk chocolate was found to be at least 50 per cent more potent than milk." The following extract from Coward's[13] paper, also from the laboratory of the Pharmaceutical Society, indicates the pitfalls of biologic experiment:

"If the degree of rickets has been very severe the metaphysis seen as an unstained gap between the shaft and the epiphysial end of the bone is very wide, and calcification ranges from a very narrow line across the metaphysis of the rat on the lowest doses of vitamin D to a thicker line on the higher doses, and even to a line so thick that it extends *practically to the base of the epiphysis and to the head of the long bone with which it fuses solidly, provided the dose of vitamin D has been large enough.*"

The union of the diaphysis (shaft) to the epiphysis (head) of a long bone by calcification of the cartilage is an evidence of cessation of growth. Such cessation of growth is seen normally when the animal reaches adult stature (as in the nineteenth to twenty-first year in man), when the animal suffers from a severe infection or when the animal ceases to grow as a result of starvation. Thus the experimental rats fed on milk chocolate were either sick, starved or adolescent. The doubtful value of such observations in relation to clinical rickets is obvious.

It is not necessary to discuss here the gradual accumulation of evidence that overdosage with vitamin D is fraught with grave risks as it promotes senescence, old age and calcification in cartilage, ligaments, tendons and the arterial walls. Overdosage with ultraviolet light, as evinced by a prolonged period of residence in the tropics for many years, has not been devoid of actuarial significance to the life assurance offices.

D. **The Color Reactions of the Vitamins.** In the annual reports of the Chemical Society, 1925, Drummond[14] stated that: "The claim by Drummond and Watson, that the long-known color reaction which cod-liver oils give with sulphuric acid can be taken as an approximate measure of their vitamin potency, has not been challenged, although it has not, as yet, received very much attention. . . . Rosenheim and Drummond have ascertained that a variety of other reagents produce colors similar in character to that produced by strong sulphuric acid, and that their intensities are *in a striking manner proportional to the vitamin A potency* as determined by feeding experiments on animals. Of the reagents giving colors, the most satisfactory are arsenic trichlorid, trichloracetic acid and methyl sulphate and their superiority over sulphuric acid rests on the greater permanence of the colors produced. It was found possible to use the reactions as approximate colorimetric methods of assay of vitamin A with an accuracy of at least the same order as that of the tedious animal tests."

In the annual reports of the Chemical Society, 1926, we read: "The color reactions described by Rosenheim and Drummond, and *believed by them* to be due to vitamin A, and possibly suitable for its quantitative estimation, have been further studied by Carr and Price, whose modifications, using $SbCl_3$ as an evaluation of the color by means of the standard glasses of a Lovibond tintometer, are great improvements."

In the annual reports, 1927, the accepted significance of the color test has extended. "Using the $SbCl_3$ test, Wilson has found that the human liver has the same high content of vitamin A as the livers of other mammals. Although the amount is rather variable fatty extracts from human liver may contain as much as 25 times the amount found in cod-liver oil."

"Rosenheim and Webster, as the result of a large series of both

FIG. 2.—Radiograms of newborn rats. The degree of ossification in the rat at birth is comparable to that in a human fetus of the fourth month.

FIG. 3.—Radiogram of a newborn guinea pig. The degree of ossification is comparable to that of a human child of seven years.

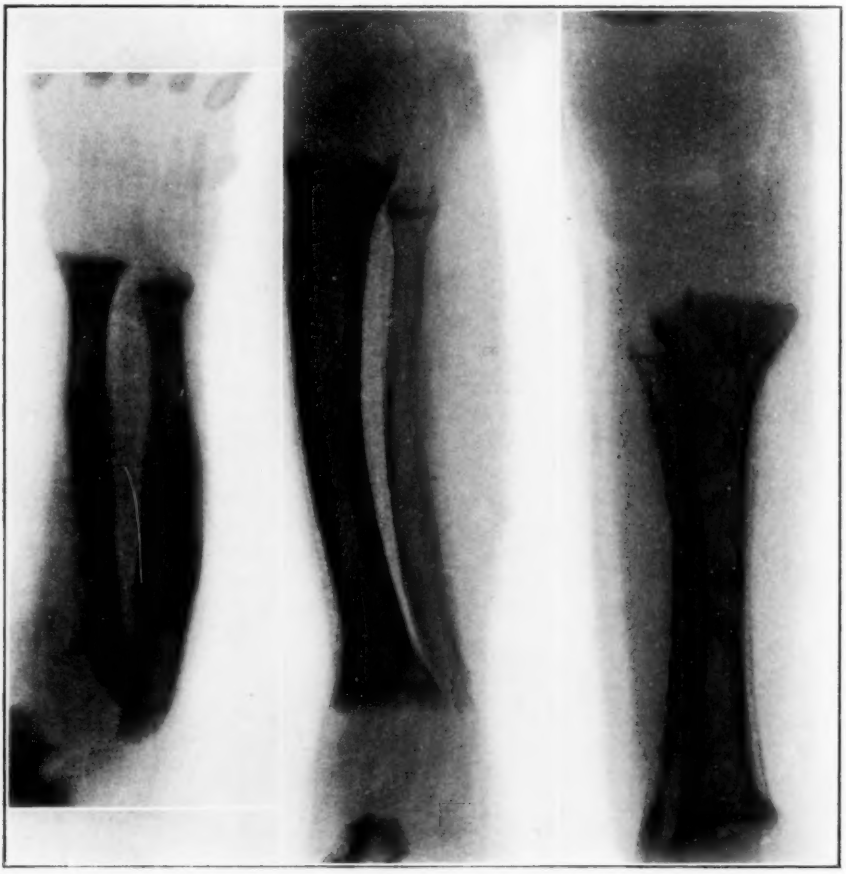

Fig. 4.—Radiogram of forearm and leg in anteroposterior and lateral views in a case of florid rickets (aged fourteen months), after treatment with 5 minims of radiosterol thrice daily for five weeks. There is no trace of the line of healing rickets.

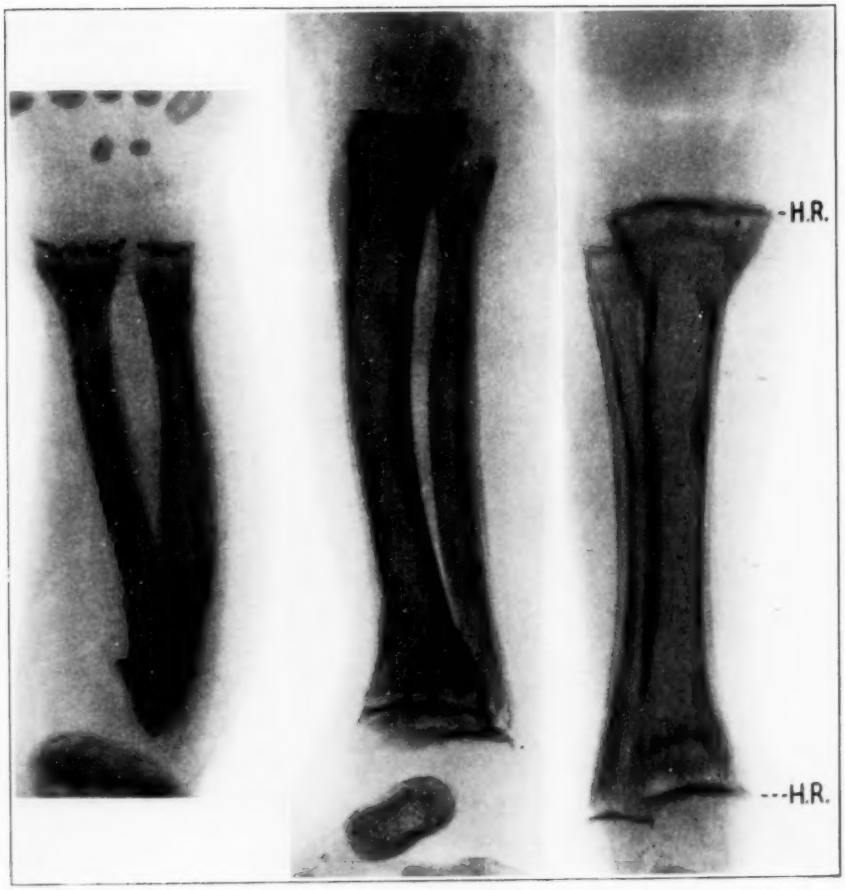

FIG. 5.—Same case as in Fig 4 after treatment with 1 dram of cod-liver oil daily for fourteen days. Note the line of healing rickets (H. R.) between the true epiphyseal cartilage and the rachitic metaphysis.

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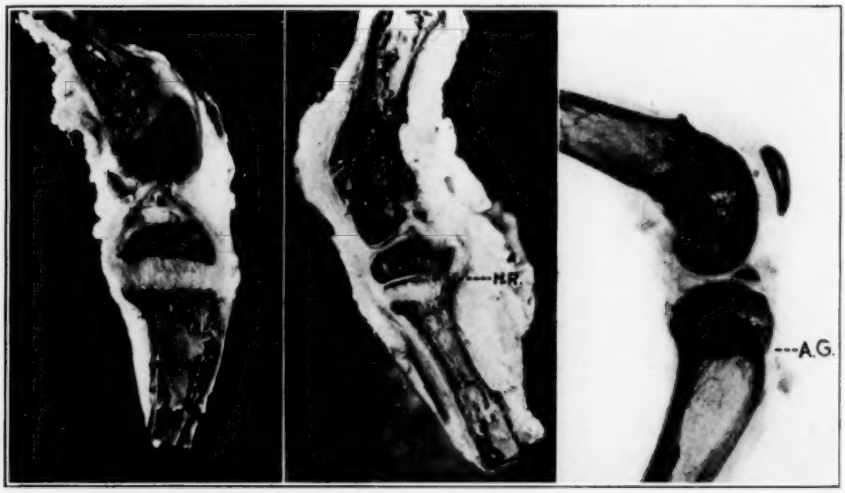

FIG. 6.—Longitudinal section of the tibia of three rachitic rats of the same litter: *a*, untreated rickets (stained $AgNO_3$) with marked increase in the width of the epiphyseal cartilage; *b*, the line of healing rickets (H. R.) clearly demarcating the true epiphyseal cartilage, after treatment with irradiated cholesterol (stained $AgNO_3$); *c*, the line of arrested growth (AG) following four days' starvation, with cessation of growth, calcification of the cartilage and almost complete union of the epiphysis to the diaphysis. Specimen cleared in oil of wintergreen.

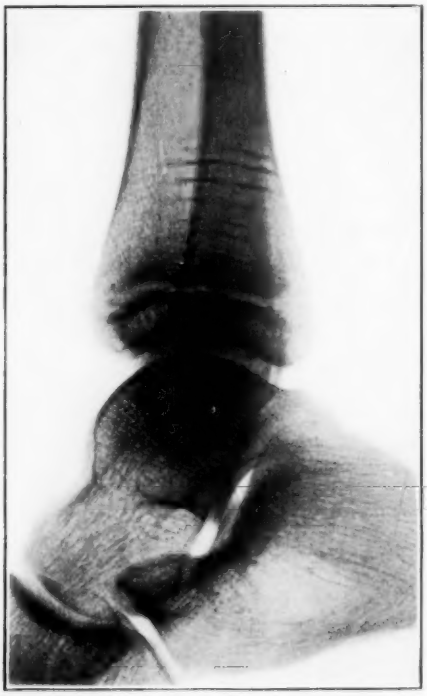

FIG. 7.—Radiogram of ankle of a diabetic girl, aged twelve years, showing lines of arrested growth laid down during exacerbations.

FIG. 9.—Radiograms of rats of four months which were placed on a rachitic diet at six weeks and maintained thereon for ten weeks without developing rickets, because the rats were already too advanced in age at the commencement of the experiment.

colorimetric and biologic tests, have found that the amount of vitamin A present in liver fats other than that of the cod, in many cases far exceeds that present in the latter source. They state that the liver oils of fishes, such as the salmon and the halibut, are often 100 times as rich in the vitamin as that of the cod. A discovery of much greater potential industrial importance is that the liver oils of herbivorous mammals, such as the sheep, calf and ox, usually contain some ten times the concentration found in the cod-liver oil. It is suggested that such mammalian oils, being free from the highly flavored clupanodoeic acid characteristic of fish oils and from the chromogen responsible for the nonspecific Fearon color reaction, are well suited for incorporation with margarine, and so constitute a ready means of raising the latter to the same standard of biologic efficiency as butter, so far as vitamin A is concerned."

The Medical Research Council Report (1926–1927) states that: "Sheep- or ox-liver fat contains from 200 to 1000 times more vitamin A than a good average sample of butter."

Much of this optimism with regard to fish oils, other than cod-liver oil, and with regard to sheep- and ox-liver fat is based on a color reaction. A color reaction has but rarely any quantitative value, and is invariably suspect to the chemist, as distinct from the biochemist. No clinician, ignorant as he is of chemistry, would estimate bile salts or bile pigments from the depth of color developed in Pettenkoffer's reaction or Gmelin's test respectively. He realizes the limits of the color reaction, and knows that the latter tests have stood but qualitatively for almost a century. Moreover, liver oils may contain minute traces of the precursors of bile salts, both of the nonsulphur containing glycocholate and of the sulphur-containing taurocholate. Wokes and Willimott[15] have recently shown that the ergosterol prepared from yeast gives with antimony chlorid blue colors very similar to the colors given by the same reagent with cod-liver oil. A variety of products related to ergosterol have been prepared, and many of these yield a blue color with antimony chlorid. Thus the color reaction is not a measure of vitamin A, since ergosterol contains no vitamin A. Until the color reaction is explained qualitatively in terms of the chromogens or other compounds involved, the whole of the work based on the assumption that the color reaction is a measure of vitamin A in liver fat or fish oils other than cod-liver oil, must be regarded as unproven. To return to the clinical aspects once again, it seems strange that such quantitative claims should be made for the potency of these mammalian liver substances in vitamin A when it is known that cod-liver oil works as a charm in human rickets. The facts of long-established clinical therapeutics are still of more significance in the treatment of rickets than the inferences suggested explicitly or implicitly by such notoriously insecure instruments as

a color reaction. Not the least among our difficulties is that biochemistry has become a business and, as the business representative of one firm of manufacturers so naïvely wrote in a letter in the *British Medical Journal* (November 3, 1928): "It would be unfortunate if the effects of vitamin D on the human organism came to be prematurely discounted at a time when the supplies are so readily available to the profession."

E. **The Chemistry of Bone.** The demand for caution in the indulgence of fanciful hypotheses is not limited to the vitaminists. The history of the problem relating to the chemistry of bone indicates the same sluggish diffusion of scientific fact, the same labored emergence of creative thought and the same inability to face the problem in hand. Kramer and Shear,[16] of New York, have recently issued a series of researches on the chemistry of bone, and they emphasize many facts which are of fundamental importance. They not only state that it is still uncertain whether triple calcium phosphate, $Ca_3(PO_4)_2$, has ever been found in bone, but also that such a compound cannot be prepared in the laboratory. In the laboratory only hydrated forms with more or less of the base can be prepared. In view of the extensive literature which has appeared in relation to the chemistry of calcium in blood and bone, it is astounding that this important fact should not have been pointed out before. Moreover, Kramer and Shear affirm that almost the whole of our theories with regard to the combination of calcium with phosphate and carbonate have been founded on the analysis of bone ash, a substance far removed from living bone. The proportion of Ca and P in bone ash led to the universal recognition of triple calcium phosphate as a constituent of the live tissue. Thus the formulæ of Hoppe-Seyler, $3Ca_3(PO_4)_2$, $CaCO_3$, and of Weiner, Wildt, Weiske, no less than that recently suggested by De Jong on the basis of Roentgen ray analysis may not represent the actual substance present in living bone.

Kramer and Shear have determined the ratio of residual calcium (that is, total calcium minus carbonate calcium) to phosphate in bones of various ages in the rat and in certain pathologic conditions, such as a calcified fibroid in man. The analyses were performed on bone that had not been burnt. The proportion of carbonate in normal rat bone increases with age. The ratio of carbonate calcium to total calcium is about 8 to 10 per cent in the bones of young rats and 15 to 16 per cent in those of adult rats. The proportion of carbonate in the bone of rachitic rats is greater than in the bone of normal rats. The proportion of carbonate in primary calcification is less than in the older bones of the same animals.

In their valuable communication Kramer and Shear state that the proportion of carbonate to phosphate has not been studied within the last thirty-five years, and they survey the history of the question from 1855 onward. From the historical point of view it

is interesting to note how much further back the problem can be traced. Von Bibra,[17] as early as 1844, published analyses of the carbonate: phosphate ratio, not in the rat, but in the human subject. His figures are, in the light of recent work, of great interest:

PHOSPHATE-CARBONATE VALUES IN HUMAN BONES (VON BIBRA, 1844).

	Total phosphate.	Calcium carbonate.
Male fetus, sixth month	55.56	3.06
Male fetus, seventh month	58.73	5.86
Child two months	58.57	6.02
Child nine months	49.33	6.12
Child five years	61.60	5.91
Woman twenty-five years	59.12	8.92
Man thirty years	60.95	7.33

These interesting results indicate a gradual increase with age in the ratio of carbonate to phosphate. That more than eighty years later similar results for the rat should be published by Kramer and Shear is an interesting example of the length of time it takes for a fact to become known.

In a recent survey of calcium metabolism Stewart and Percival[18] have indicated that our knowledge is still fragmentary, and they deal in detail with the significance, if any, of the variation of the calcium content of the serum. In the account of the best attested alteration of the serum calcium, as seen in pregnancy, they indicate the marked incompatibility of the results of various observers. In women several observers have reported a fall in the maternal serum calcium during the later stages of pregnancy. In rabbits a sudden fall a few days before parturition is reported. Various observers, using different experimental animals, show a surprising lack of unanimity. "Harding, summing up the position, thinks the balance of evidence shows that there is a slight decrease in the serum calcium during the later stages of pregnancy, a conclusion which is in accord with the results of Vignes and Coisset, that in guinea pigs there is a progressive decalcification throughout the period of gestation, and with those of Sherman and MacLeod, that in female rats a distinct lowering of the percentage of calcium in the body occurs as the result of suckling."[18]

The above quotation illustrates the extent to which the chemist and the biochemist may become lost in a maze of analytical figures when ignorant of the fact that the various experimental animals have a generic, specific and individual "biochemistry." It is a well-known anatomic fact that the rat fetus is born naked, blind and helpless after a gestation period of twenty-one days, with its skeletal ossification barely commenced. The newborn rat (Fig. 2) possesses what is virtually a cartilaginous skeleton, comparable to that of a human fetus of the third month, and ossification proceeds rapidly after birth. On the other hand, the guinea pig is born (Fig. 3) in a precocious stage of development. The eyes are open,

body well covered and skeletal ossification advanced to a degree comparable to that of a seven-year-old child. *Thus, on the maternal rat there is a demand for calcium during lactation, whereas on the maternal guinea pig the demand occurs during pregnancy.*

The apparent incongruities of the problem of calcium metabolism in the pregnant and lactating mother are readily interpreted with the aid of a knowledge of that morphology which is today so despised. There is a tendency to regard animal morphology as an exhausted subject, and biochemistry as a recently established science with a peculiarly potent armamentarium. It requires but little thought to see that the processes of growth and repair in the animal economy are still essentially physiologic, no less than that the factors in reproduction and heredity are also physiologic. It is refreshing to note that even as far back as 1843 Lehmann, in his textbook, *Physiologic Chemistry*, states:

"The analysis of bone is undoubtedly one of the simplest operations of *zoöchemical* research, but so many different methods have been attempted that, notwithstanding the great number of analyses, we have arrived at no conclusive results; we see, for example, that the chemical composition of the phosphate of lime contained in the bones is still doubtful, even at the present time."

Read "biochemical" for the earlier "zoöchemical" and 1928 for 1843, and the criticism still stands.

F. **The Vitamins in Bone Formation.** I have previously shown[2] that the problem of growing bone may be analyzed in terms of three distinct processes: the growth of cartilage, the calcification of cartilage and true bone formation. The characteristics of these three processes may be briefly summarized as follows:

1. *Growth of Cartilage.* Cartilage is a relatively simple undifferentiated tissue in which the actively proliferating cells are separated by a matrix which is perfused by tissue juice for the nutrition of the cells. There is no well-developed blood vascular system in cartilage. The proliferation of cartilage resembles in many respects the proliferation of bacteria, yeast, vegetable cambium and the growth of a gumma, tubercle or avascular tumor. Just as there is a limit to the size of a gumma, tubercle or tumor, so there is a limit to the size of a colony of cartilage cells which can continue to proliferate by imbibition of the tissue juice. All growth of this type, sheer vegetative proliferation, depends in particular both in the animal and vegetable world, on a supply of water-soluble products. Among these products are the water-soluble vitamins, such as vitamin B (B_2 of Peters or P–P of Guldberg). In the classical experiments on tissue culture, Burrows[19] has postulated in the nutritive fluid the existence of a water-soluble product, which he termed "archusia"—the ancient growth-promoting substance. Carrel[20] has expressed the same idea and has designated the substance or substances "trephones."

2. *Calcification of Cartilage.* When any of these proliferating tissues reach the limit of growth the nutrition of part of the colony becomes precarious, and those cells which are so situated topographically as to feel the dearth of food become senile. Thus, for example, the cells at the center of the mass of cartilage at the lower end of the femur in the human fetus near term show signs of old age. In the cambium of plants old age is heralded by the conversion of cambium into phloem and xylem, the woody vessels of the latter subserving the purpose of a dead vascular system in the live plant. In carcinomata old age is indicated by hyalinization and cell-nest formation. In the gumma, tuberculoma and in cartilage the changes are essentially senescence of the cell with calcification of the matrix. Thus the conversion of live young cambium to woody vessels, the changes in avascular tumors and granulomata, the changes in the thymus, in the placenta and in the fibroid, no less than the changes in the proliferating cartilage are manifestations of senescence and death.

Throughout the animal world and the vegetable world senescence is accompanied by calcification or degenerative changes strictly comparable thereto. Thus, there is for each vertebrate a definite limiting size to which a mass of cartilage can grow. This is a specific character. Any departure therefrom is pathologic. Disease presents a comparable phenomenon in the limit of size imposed upon a gumma or tubercle in man.

The process of senescence in cartilage due to nutritional inadequacy in the absence of a blood vascular system can be controlled by vitamin D, sunshine, ultraviolet light or any irradiated sterol such as ergosterol. This action is not only specific for growing cartilage, but for vegetable cambium. Every gardener knows that exposure of a plant such as the broad bean to vigorous sunshine leads to stunting of growth, conversion of the cambium into woody stem and speedy flowering. The process of senescence is speeded up by vitamin D, ultraviolet light or ergosterol.

The main commercial source of vitamin D today is the ergosterol manufactured from baker's yeast extract. Yeast contains fat, and the fat-soluble vitamin D is associated therewith. All plants exhibit this type of senescence and contain traces of oil or fat and associated substances comparable to vitamin D.

Clinically, and the life assurance offices were not slow to recognize this, residence in the tropics with exposure to undue sunshine leads to premature senescence in the white man. The process of calcification invades the ligaments, tendons, the media of the bloodvessels and the meninges. Overdosage of experimental animals with vitamin D leads to premature senescence by the symptomatic deposition of calcium in the proliferative tissues. To what extent the recent experimental work is dependent upon coincidental infection in addition to the overdosage with vitamin D is yet to be determined.

Thus in the normal growing animal calcification of cartilage, and nothing more than calcification, is controlled by vitamin D, sunshine, ultraviolet light or ergosterol.

3. *Bone Formation.* The higher forms of life are characterized by a multiformity of parts for a diversity of function, for to them has fallen, as Aristotle so clearly stated, not only life, but life in a high degree. Thus mere vegetative proliferation has given way to differentiation for function. The cell of the sweat gland in man does not proliferate, but pours out sweat for seventy years. The heart muscle cell does not breed but beats for three score years and ten. The liver cell adopts the rôle of chief chemist, the cell of the islet of Langerhans controls sugar metabolism and the cell of the kidney tubule becomes and stays an expert on hydrogen-ion concentration. The power of regeneration is not entirely lost in the case of the liver or peripheral nerves, but is entirely absent in the brain and dermis proper.

The mass of calcified cartilage, whether in the shaft of the long bone of the embryo, or in the epiphysis of the child, approaches senescence and a resting stage comparable to that seen in spore formation by certain bacteria. This virtually dead calcified cartilage acts as a foreign body, and calls forth a mechanism which has much in common with aseptic inflammation. An eruption of bloodvessels takes place, and two new highly vascular tissues are laid down, *viz.*, bone and marrow. Bone and marrow are highly differentiated tissues designed for widely specialized functions and richly supplied with a vigorous capillary network. The osteoblast or bone cell appears only in the neighborhood of a rich vascular supply. Whether the origin of the osteoblast be from primitive connective tissue, perivascular connective tissue, the rete of the bone marrow or from the sudden rejuvenescence of those senescent cartilage cells at death's door, the one fact emerges: a fully differentiated osteoblast, able to control the deposition and absorption of bone, able to contribute to calcium metabolism, able to repair injury, such a working cell in the glory of its full differentiation for function appears only in the region of young capillaries in the presence of an adequate supply of blood-borne fat-soluble vitamin A. If the supply of vitamin A be limited, the degree of differentiation of the osteoblast is decreased, and osteoid tissue is laid down instead of true bone. If the supply of vitamin A be still further diminished, the degree of differentiation is minimal and fibroblasts alone are formed.

The function of fat-soluble vitamin A is the control of the differentiation of the tissue for adequate function. This applies not only to bone but to all tissues. The clinical picture of rickets in the child exhibits this clearly, as so eloquently described by Steinhauser, in 1840. Mellanby's statement[1] of the anti-infective rôle of vitamin A is but a rider to this function of vitamin A which was stressed

by Harris, in 1926,[2] when he stated: "The term 'growth-promoting' as applied to vitamin A is a misnomer," and "this (vitamin A) is the substance that is concerned with differentiation."

As in the case of the water-soluble vitamins concerned with growth, the experiments of Burrows and Carrel were confirmatory in terms of archusia and trephones, the primitive growth-promoting substances, so in the case of the other vitamins there are pertinent points of contact with work in other fields. Robison's experiments[21] *in vitro* on the calcifying enzyme indicate that hexosephosphoric esters play a part in controlling the deposition of calcium in the matrix of senescent cartilage. Further, Burrows in his tissue-culture experiments stated that differentiation of the tissue depended on a fat-soluble substance or group of substances to which he gave the name "ergusia"—the energy-producing substance, as distinct from "archusia," the primitive growth-promoting substance.

In 1841 Lehmann and Marchand[22] called attention to the fact that the rachitic bones of infants on boiling yielded less gelatin than normal bones. This acute observation is clearly explicable today, inasmuch as they were dealing with the bones from a case of healed rickets. The dense hard bone of healed rickets yields much less collagen than cancellous bone, white fibrous connective tissue or skin.

Rickets is a disease involving all three processes above described. The proliferation of cartilage is excessive, the calcification of the cartilage is defective and the differentiation of true bone is imperfect. The three processes are in part controlled by water-soluble vitamin B, fat-soluble vitamin D and fat-soluble vitamin A respectively. The healing of rickets calls for a balance in all three processes with a balanced supply of all three vitamins. Neither can effect a cure in the absence of the others. Hence, the pretensions of the adherents of one or other vitamin are inherently false, and cod-liver oil alone gives a consistently cheap, adequate and balanced supply of both the calcifying vitamin D and the differentiating vitamin A. This appears to be the legitimate explanation of the marked superiority of cod-liver oil over any of the advertised substitutes.

The two radiograms (Figs. 4 and 5) in a severe case of acute human rickets show the effects of treatment with: (1) Ergosterol, maximum dose of 5 minims three times a day for five weeks; (2) cod-liver oil, 1 dram daily for ten days. There is no question as to the marked superiority of cod-liver oil. Treatment with radiosterol for an extended period failed to delineate the line of healing rickets. On the other hand, the response to cod-liver oil was rapid and dramatic, and was reflected in the condition of the patient. No better example could be wished for to illustrate the exact topographic characters of the line of healing rickets (H. R., Fig. 5).

G. **The Comparative Biology of the Vitamins.** Fish are essentially of three kinds as regards fat deposits. In the one group,

such as the mackerel and herring, the fat is almost uniformly distributed throughout the muscles and liver; in the other group, such as the cod, hake and whiting, the flesh is relatively free from fat, and the fat is concentrated in the liver. In the third form, such as the eel, there is a marked accumulation of the fat around the peritoneum, so that the ovaries and testes are dissected out with great difficulty from the mass of fat. As regards offspring, fish can be divided into two groups, the one such as the dogfish lays about 100 large eggs, the rate of laying not differing much from that of the domestic hen. The other, such as the herring and cod, lay a large number of eggs of small size in the minimum of time. In the case of the cod the number of ova spawned exceeds 10,000,000 and may reach 13,000,000. In this extreme fecundity of the codfish lies the whole problem of the potency of cod-liver oil in therapeutics. The eggs of the cod are not destined to grow up into undifferentiated masses of protoplasm, but into bony fish with vertebral column, muscles, liver, spleen, kidney, cœlum and a blood vascular system. The codfish has acquired the power of concentrating in its liver for delivery to the ova, sufficient of the fat-soluble vitamin A to guarantee differentiation of the tissues during the early stages of growth to a family of 10,000,000. Thus, the potency of the liver oil is virtually proportional to the number of the offspring, to the degree of differentiation in the offspring, and to the extent to which the fat depot is concentrated in the liver.

Not only is cod-liver oil extremely rich in vitamin A, but also in vitamin D, for in the economy of the tissues a proliferative tissue such as cartilage is not converted directly into bone, but is first projected through the stage of senescence involved in calcification and controlled by vitamin D. In no case does true bone adjoin cartilage without the presence of an intervening zone of calcified cartilage.

The amount of fat-soluble vitamin A in plants is, in accordance with their small degree of differentiation, small. The degree of differentiation is but that necessary to differentiate root from shoot, and to control the processes involved in seed formation. On the other hand, water-soluble vitamins are richly distributed in plants, for this year's seed has in its store vitamin B to guarantee the growth of next year's plant. Vitamin A proper is essentially distributed in greatest concentration in those cœlomate animals with a vascular system, hemoglobin and maximum differentiation. It has reached its maximum concentration in that fish, the cod, which waxes and multiplies so inordinately.*

* That the power of concentration of the vitamins is related to the prolificity of the parent as instanced in the codfish and in spinach, receives collateral suggestiveness from the recent work by Bracewell, Hoyle and Zilva on the distribution of vitamin in apples. They find that the antiscurvy potency of vitamin C varies with the type of apple, reaching a maximum in Bramley's Seedling, a variety grown by reason of its productiveness.

The cycle of vitamin A and of vitamin D is not a peculiarly vegetable cycle. The organisms of the plankton do not live exclusively on chlorophyll-containing algæ. They eat small fish, and innumerable eggs, realizing that animal food affords a much more concentrated supply of vitamin D and vitamin A. This explains the fondness of vegetarians for eggs, milk and butter, all foods rich in vitamins A and D. It also explains the frequency with which they, the vegetarians, are compelled to resort to cod-liver oil.

The peculiar manner in which primitive people have arrived at comparable if not identical methods of treating disease in widely separated geographic areas is illustrated in the case of osteomalacia, which is widespread in Kashmir. According to Vaughan,[23] "There are three indigenous Kashmiri cures for 'trouble in the bones:' (1) A special clay called Baramulla earth, rich in calcium phosphate; (2) pills made of fish liver; (3) rubbing with mustard oil and exposing to sunlight." The popularity of caviare in Russia and Central Asia is probably due to the empirical belief in its potency in malnutrition during the winter months when milk and butter were scarce.

In relation to the astounding fertility of the cod and its bearing on the cycle of vitamin A, it is interesting to note that the plants which are relatively rich in vitamin A, although the content is much less in the vegetable world than in the animal world, are those very plants which man has cultivated because of their natural prolificity. The whole of the cabbage family, lettuce, spinach, the cultivated grasses, such as oats, barley and wheat, are characterized by yielding a number of seeds per plant ranging from 5000 to 500,000.

Last, it must be stressed that there is still room for a purely chemical aspect of the vitamin problem in terms of the salt content of the diet. The rôle of phosphorus and phosphates in therapeutics no less than in the manuring of the fields is an ancient concept. Many workers have claimed that rickets could be controlled by a suitable balance of the calcium and phosphate intake. The various forms of glass permeable to the ultraviolet rays owe their properties to the admixture of small quantities of calcium phosphate. A most fundamental contribution to our knowledge has been made by the recent Discovery Expedition (H. M. S. Stationery Office, 1929), in which it is pointed out that the distribution of diatoms, shrimps and whales is greatest there where the phosphatic content of the sea water is a maximum. Thus, it would appear to be quite as rational to worship the phosphatic ooze of the ocean bed as to worship the ultraviolet rays of the sun.

H. **The Line Test for Healing Rickets.** In 1922 McCollum, Simmonds, Shipley and Park[24] published an account of their line test for healing rickets. Rats were placed on a rachitic diet, high in calcium, low in phosphorus, for six weeks. On administration of

any antirachitic substance a line of calcification appears on the epiphyseal side of the abnormal cartilaginous metaphysis. The line can be brought into prominence by staining with $AgNO_3$, and may, especially in the larger animals, be clearly demonstrated on the radiogram. This valuable laboratory test is based on the dictum of Schmorl,[25] who, as far back as 1909, had stated that the wide cartilage zone in rickets showed healing there where calcium would have been deposited if the animal had not had rickets. This line is clearly demonstrated in the longitudinal sections of the tibia in (*a*) rachitic rat and (*b*) rat treated with cod-liver oil. (Fig. 6.) The line of healing rickets (H. R.) is clearly delineated, and is bounded on the epiphyseal side by an epiphyseal cartilage of normal width, whereas on the diaphyseal side it is bounded by the redundant excess of cartilage which characterizes the rachitic zone (*a*). The exact topographic anatomy of this line of healing rickets must be emphasized as its presence in any given case is the only clear proof of the healing effect of vitamin D in the diet, or of the healing effect of ultraviolet light.

McCollum and his coworkers stated: "This test may be used to determine the ability of any agency to heal rickets." Correctly speaking, the line is not a test of the ability to heal rickets, but is a test of the ability to calcify cartilage, this being but one of the factors necessary to heal rickets. The test is positive with sunshine, ultraviolet light, ergosterol, butter, eggs and cod-liver oil. It is a sound test for the calcifying vitamin D, but gives no information at all about bone formation and true osteogenesis which is dependent upon vitamin A. Thus the line test is a test for calcium deposition in cartilage, not for differentiation of true bone.

The morphologic significance of the exact site of deposition of calcium is evident if we consider the nutrition of the diaphysis and epiphysis. William Hunter pointed out that the blood and lymph supply of the epiphysis is distinct from that of the diaphysis, there being no anastomoses between the nutrient artery of the diaphysis and the *circulus articuli vasculosus*, which supplies the joint and the epiphysis. This is recognized by the surgeon as a prime factor in the localization and spread of tubercular and osteomyelitic infections. When, as in human rickets, the cartilaginous zone of the growth cartilage is increased in width from about 1 mm. in the normal to 2 or 3 mm. in the rachitic, the area in the cartilage which is faced with the maximum nutritional difficulty is that marked H. R. (Fig. 6, *b*). The true epiphyseal cartilage on the epiphyseal side of H. R. is nourished by the circulus vasculosus, and the pathologic rachitic cartilage of the metaphysis, on the diaphyseal side of H. R., is nourished by imbibition of tissue juice from the territory of the nutrient artery of the marrow and shaft. Thus H. R. is a zone of minimum nutrition, and here it is that senescence and calcification of the cartilaginous matrix occurs. The site of depo-

sition of calcium is determined by the nutritional factor, in exactly the same way as the site of deposition of calcium in the epiphysis itself occurs at the site of minimum nutrition. This explains the actual position of any of those points of calcification and subsequent ossification in the skeleton which we term ossification centers.

The complete block or absence of anastomoses between the vascular fields of the diaphysis on the one hand and the epiphysis and joint cavity on the other is only equalled by the block between pylorus and duodenum in the gut, and by the blocks in the brain, liver, spleen and kidney which are responsible for the designation "end arteries" and for the phenomenon of infarction. This observation is by no means original, for Rindfleisch,[26] in his textbook of *Pathologic Anatomy* (1870), in reference to "that *perversion* of growth which constitutes rickets," states: "For us the important point is that the earthy salts are first deposited along those neutral lines which may be looked upon with equal justice as the *limitary* or axial lines of the vascular territories."

The reason for stressing the morphologic aspect of this line of healing rickets is twofold. In the first place, I have attempted repeatedly to emphasize that the radiograms of children and of experimental animals frequently exhibit transverse lines of arrested growth which must not be confused with the line of healing rickets. The characters of the line of arrested growth resulting from acute illness or starvation, as compared with the line of healing rickets, are adequately shown in Fig. 7.

Second, a recent article appeared in the *Lancet*,[27] "The Vitamin Content of Margarine," with the hallmark of the Pharmaceutical Society, stating that the given margarines are equal to the best summer butter in their vitamin A and D content. The animals employed on the experiment were rats. In Fig. 8 *not one of the rachitic animals shows the line of healing rickets.* Each figure can be interpreted only as an example of that "self-healing" of rickets which occurs when an animal is on an inadequate diet or suffers an acute infection. This is strictly comparable to the "self-healing" of untreated rickets which occurs in the child of the slums, whereby the actively growing rachitic baby of more than average weight is gradually converted into the slow-growing "starveling" with permanent deformity of the long bones. Moreover, in none of these experiments, either in the direction of margarine or milk chocolate, has any attempt been made to examine the structure of the bone, either grossly, radiographically or histologically. The mere deposition of calcium in the rachitic zone of cartilage is but a step, although a necessary one, toward the final process of osteogenesis. None of the experiments give any information as to the vitamin A content of the food concerned, and such work will remain valueless until the clinical symptoms of human rickets are appreciated by the biochemist.

The experimental rickets of rats is produced either by a diet rich in calcium and poor in phosphorus, by a diet poor in calcium and rich in phosphorus or by substituting magnesium or strontium for calcium, the other constituents of the diet being relatively deficient in vitamins D and A. Much work has yet to be done in the correlation of the experimental rickets of the rat with the clinical rickets of man. The difficulty in producing experimental rickets in the guinea pig, rabbit and cat calls for a greater degree

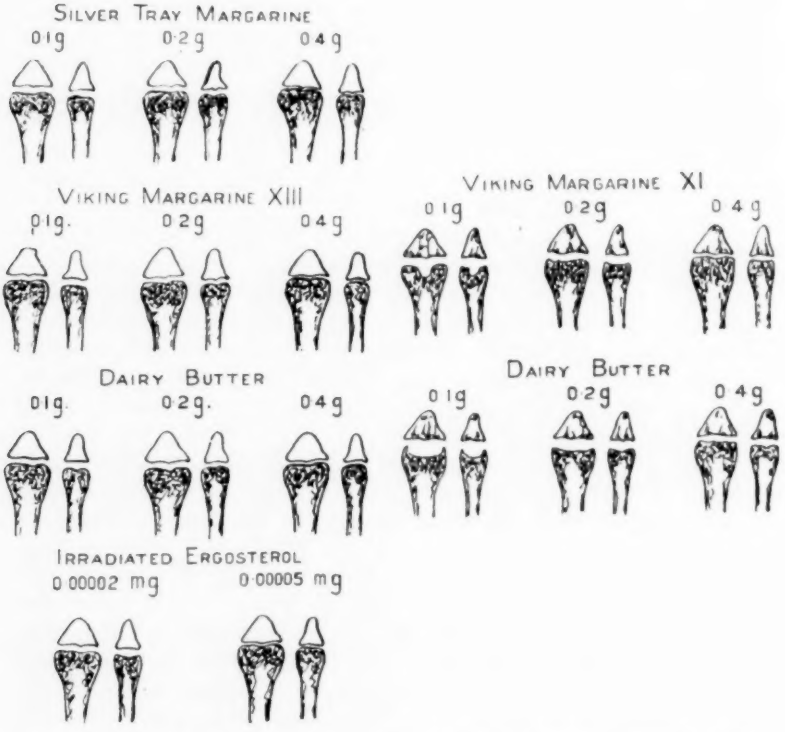

Fig. 8.—Copies of illustrations from Coward's paper (Lancet, October 8, 1928). In no single case is there any line of healing rickets. The claims as to the antirachitic potency of the foods concerned are therefore invalidated.

of caution in transferring experimental results from laboratory animals to the problem of clinical rickets in man. In an extended study of rickets produced in rats by the administration of a diet rich in calcium and low in phosphate, Karelitz and Shohl[28] have rightly drawn attention to the fact that the question of the deposition of phosphate may be of more significance than the problem of deposition of calcium, and have shown that addition of phosphate to the diet leads to extremely rapid healing of the rickets. But this

interpretation of the rôle of additional phosphate in promoting healing is vitiated by the fact that in all cases of addition of phosphate to the diet the rats ate only a half of the normal ration. Thus the "healing" was not due solely to the effect of the phosphate in restoring the salt balance, but was largely attributable to the fact that the rachitic animals during a period of rapid growth were converted into starved nongrowing animals, and so the rickets healed by that process of arrested growth which has to be so clearly distinguished from healing rickets as such.

It is a well-known clinical fact that human rickets is strictly limited as regards the time of its appearance to the first two years of life. Irrespective of diet or surroundings, it is impossible to produce rickets in a child after two years of age. Changes in the bones in any way resembling those of rickets are seen with extreme rarity only during the period of rapid growth associated with puberty. For this reason it is important to determine for the rat and the pup the exact limits of the ages during which susceptibility to rickets exists. In the case of the rat the age is below five weeks, and in the pup it is probably less than ten weeks. The radiogram (Fig. 9) illustrates the failure to produce rickets in rats which were placed on a rachitic diet at six weeks and left on that diet for a period of three months. The neglect of this clinical fact, that there is a strictly limited age at which rickets can be produced, vitiates many of the published experiments, such as those of Bacharach.[12] Nothing is to be gained by clouding the issue in terms of storage or reserve of vitamin. The age of the animal at the commencement of the experiment must be stated.

Conclusion. From a consideration of the history of the vitamins, and of the train of idiosyncrasies therein entailed, from color reaction, the chemistry of bone and the kaleidoscopic changes of viewpoint stated by interested manufacturers, from the theory of the rôle of the vitamins in bone formation and from the theory of the peculiar efficacy of cod-liver oil in the treatment of rickets, there emerges this one fact. The most reliable weapon in treatment of rickets is cod-liver oil. The recognition of the merits thereof is not due to any specific contribution to clinical medicine in these days, but, as is the case with so much in life, is part of the wonderful clinical heritage of the past.

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ABSORPTION OF CALCIUM FROM THE GALL BLADDER.

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In 1928 there appeared a communication from Wilkie[1] in which it was reported that in the studies on experimental cholecystitis in rabbits cholesterin stones were formed if the cystic duct remained

patent, but, in cases where the cystic duct was closed, experimental cholecystitis produced both by intravenous injections and by mural injections of streptococci gave rise to stones containing a high percentage of calcium. From these studies it became evident that the gall bladder's ability to absorb calcium should be investigated and therefore the following experiments were undertaken.

The results of our estimations of calcium content of the bile are all charted on the accompanying tables. It was found that the method of Kramer and Tisdall as modified by Clark and Collip[2] for determination of blood calcium yielded consistent results when it was applied to bile. All of the estimations were made by this method. It was not even necessary to use any more washing of the precipitate than one uses in the estimation of calcium in the blood in most cases. When, however, the bile was very thick with mucus or pigment, one or two additional washings cleared the precipitate. The results of these experiments will be considered under the following headings:

TABLE I.—CALCIUM CONTENT OF GALL-BLADDER BILE.

Exp. No.	Days P. O.	Procedure.	Bile calcium, mg. per 100 cc.
1	0	Normal control	34.1
2	0	Normal control	38.4
3	0	Normal control	36.2
4	0	Normal control	61.4
5	0	Normal control	46.6
6	1	Cystic duct tied	50.8
7	1	Cystic duct tied	44.4
8	3	Cystic duct tied	20.3
9	3	Cystic duct tied	42.0
10	3	Cystic duct tied	36.2
11	4	Cystic duct tied	38.6
12	17	Cystic duct tied	46.3
13	3	Cystic and common duct tied	54.3
14	4	Cystic and common duct tied	16.0
15	8	Cystic and common duct tied	53.0
16	8	Cystic and common duct tied	47.2
17	12	Cystic and common duct tied	40.4
18	20	Cystic and common duct tied	35.6
19	3	Common duct tied	38.4
20	3	Common duct tied	48.2
21	3	Common duct tied	22.1
22	3	Common duct tied	41.6
23	3	Common duct tied	52.8
24	30	Common duct tied	36.2
25	3	Common duct tied and right nephrectomy	44.3
26	3	Common duct tied and right nephrectomy	46.2
27	8	Common duct tied and right nephrectomy	41.3
28	10	Common duct tied and right nephrectomy	46.4

1. *Calcium Content of the Liver Bile and the Gall-bladder Bile.* Fasting animals were anesthetized with ether and their abdomens opened. The cystic duct was promptly clamped before any manipulation of the gall bladder occurred which was liable to cause it to empty. The contents of the gall bladder were then aspirated.

Then the common duct was sectioned and a cannula inserted into the proximal stump and the dog kept alive until sufficient liver bile had been accumulated for purposes of estimation. It can be seen from Table II that the content of calcium of the liver bile varied between 20.1 and 11.4 (the average content being 14.6) mgs. per 100 cc. The content of the gall-bladder bile varied between 59.1 and 40.4 (the average being 52.3) mgs. per 100 cc. These figures indicate the concentration of bile in the gall bladder brought about by the absorption of water in the viscus. It has been variously stated that this concentration varies between 6 and 10 times, probably averaging in the neighborhood of 8. As measured in calcium concentration, our statistics show it to be only about $3\frac{1}{2}$ times, which seems to be slight evidence that a certain amount of calcium as well as water is absorbed by the mucosa of the gall bladder.

TABLE II.—CALCIUM IN LIVER AND GALL-BLADDER BILE.

Exp. No.	Procedure.	Liver bile.	Gall-bladder bile.
1	Normal control	16.3	47.4
2	Normal control	20.1	40.4
3	Normal control	11.4	56.0
4	Normal control	12.8	58.2
5	Normal control	12.2	59.1

TABLE III.—EFFECT OF PROLONGED CYSTIC DUCT OBSTRUCTION ON CALCIUM IN GALL-BLADDER BILE.

Exp. No.	Days P. O.	Procedure.	Bile calcium, mg. per 100 cc.
1	1	Cystic duct tied	37.3
	56	Cystic duct tied	19.4
2	1	Cystic duct tied	58.2
	56	Cystic duct tied	38.2

TABLE IV.—SUMMARY OF CALCIUM FINDINGS IN VARIOUS BILES.

Exp No.		Calcium, mg. per 100 cc.
5	Liver bile	14.6
10	Gall-bladder bile	47.7
11	Gall-bladder bile after cystic duct ligature	39.2
6	Gall-bladder bile after common and cystic duct ligatures	41.6
6	Gall-bladder bile after common duct ligature	39.9
4	Gall-bladder bile after common duct ligature and right nephrectomy	44.5

2. *Effect of Cystic Duct Ligation on Gall-bladder Bile.* By referring to the Tables I and II one sees that normal dogs were electrocuted after twenty-four hours' fasting. In 10 cases, the average concentration of calcium in the gall bladder was 47.7 per 100 cc. In contradistinction to this, one can compare the series of calcium estimations made upon gall bladders in which the cystic duct had been ligated for various periods of time as shown in Tables I and III. An average of 11 such cases gave the figure of 39.2 as

the average calcium content of bile after ligature of the cystic duct. This again is evidence that there is a resorption of calcium from the gall bladder and that, although it is not absorbed as rapidly as water, the concentration tends to become about 20 per cent less in a few days after ligature of the cystic duct.

3. *Long Period Resorption of Calcium.* As further evidence of resorption of calcium from the gall bladder, one is referred to Table III. In these 2 dogs a sample of gall-bladder bile was withdrawn twenty-four hours after ligature of the cystic duct and again fifty-six days later when the animals were sacrificed. Although it was not possible to measure the total amount of fluid in the gall bladder, it was in both cases obviously less, the gall bladder appearing very much smaller in the period of the latter observation. In spite of this fact, the calcium in the gall bladder bile in 1 case dropped from 37.3 to 19.4 mgs. per 100 cc. and in the other from 58.2 to 38.2 mgs. per 100 cc. In 6 others both the common and cystic ducts were ligated and the average content of the gall-bladder bile was 41.6. In 4 other dogs the common duct was tied and a unilateral nephrectomy performed. This procedure brings about a marked intensification of the jaundice and the average calcium content of the bile in these cases was 44.5 mgs. per 100 cc.

In each group of experiments which we have thus reported, the average calcium content of the bile was less than that in our normal controls. Jaundice did not seem to influence the figures appreciably.

4. *The Influence of Infection.* In these experiments infection of the gall bladder often took place after stasis of the bile had been produced. The results of the pathologic and bacteriologic studies on these gall bladders are being reported elsewhere. In 4 cases, however, actual empyema of the gall bladder was found, these were Nos. 8, 14, and 21 on Table I and No. 1 on Table III. In each of these cases the bile calcium had reached very low levels quite comparable to that found in normal liver bile.

Discussion. These experiments were performed upon dogs and perhaps are not strictly comparable to the work reported by Wilkie who used rabbits. However, the amount of bile recoverable from rabbits is not large enough to permit chemical examination of the calcium and therefore we must consider the difference in species of the animal as being possibly the reason for the contradictory results. Wilkie's results are difficult to explain unless one can demonstrate a higher concentration of calcium in the gall bladder after the ligature of the cystic duct. In all of our experiments here reported the exact opposite was the case and our results indicate that, although the resorption of water takes place most rapidly, there seems to be a gradual resorption of calcium also from the gall bladder and that this resorption tends to be accentuated and accelerated if marked suppuration of the gall bladder takes place.

These results are in accord of those of Peyton Rous and his asso-

ciates, who showed that there was an enormously higher concentration of bilirubin by the gall bladder than of calcium, and therefore concluded that the latter was absorbed.[3,4]

Conclusion. In cystic duct obstruction in dogs, the relatively high calcium content of the cystic duct bile is gradually lowered and in the presence of infection it is rapidly lowered.

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RHEUMATIC PERITONITIS.

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It is becoming increasingly apparent that rheumatic fever is a disease whose lesions may affect many different tissues throughout the body.[1a] Its particular predilection for endothelial surfaces (the synovial membrane, endocardium, pericardium, pleura and even the intima of bloodvessels[1b]) has long been recognized. In view of this fact, the relative invulnerability of one of the largest of these, the peritoneum, has frequently excited comment. The following case report and review of the literature deal with the question as to whether rheumatic invasion of the peritoneum does occur.

Case Report. S. C., a Jewish girl, aged thirteen years, was admitted to the hospital of the University of Pennsylvania on April 28, 1928. Since 1926 she had experienced recurring attacks of tonsillitis and had complained of "growing pains" at intervals. She had never suffered from acute rheumatic fever nor chorea. There had been occasional attacks of abdominal pain and fever, an adequate description of which is not available. She had never menstruated. For some time prior to April 22, 1928 she had been enjoying good health. On that day she began to have diarrhea and mild bilateral lower abdominal pain. On April 26, nausea and vomiting developed, and the abdominal pain became more severe. Ingestion of food increased the pain. The diarrhea continued. On admission six days after the onset, the temperature was 103.3° F.; pulse, 150; respirations, 24. The patient was thin and dyspneic. The tongue was dry and

coated, the teeth were in good condition, the tonsils were small and not remarkable in appearance. There were marked arterial and venous pulsations in the neck. There were no abnormal physical signs over the lungs. The blood pressure was 110 systolic and 60 diastolic. The heart was markedly enlarged, the apex impulse being prominent and located in the anterior axillary line. There were signs of mitral stenosis and insufficiency and of aortic insufficiency. The abdomen showed no distention. There was marked bilateral lower abdominal rigidity and exquisite tenderness. No peristaltic sounds were audible. No organs nor masses were palpable. Rectal examination revealed generalized tenderness in the pelvis. There was no vaginal discharge. The leukocyte count was 28,200; the hemoglobin, 68 per cent (Sahli). Urine analysis showed a specific gravity of 1.020, acid reaction, a heavy trace of albumin, no sugar, occasional hyalin casts, 1 or 2 leukocytes per high-power field and no erythrocytes. The patient's condition was diagnosed as "probable acute appendicitis with possible rupture and pelvic peritonitis," and operation was undertaken on this basis.

The abdomen was opened by one of us (E. L. E.) through a McBurney incision. On separation of the transversalis muscle, the subperitoneal tissues and outer surface of the peritoneum were found to be acutely edematous and hyperemic. On opening the peritoneum, clear fluid escaped in abundance. The inner surface of the peritoneum was edematous, beefy, red and velvety as far as it was explored. There were circumscribed areas of intense edema which looked like large urticaria, beneath the parietal peritoneum, throughout the operative field and down in the pelvis. No suppurative focus was found in the gut, uterus or appendix to explain these phenomena. On account of the severe inflammatory reaction, it was thought that pus must be present, and since it was not found within the abdomen, the peritoneum was stripped from the muscles down into the pelvis and out into the flank, in a search for an extraperitoneal collection. No pus was located by this procedure, so, after a routine appendectomy, the abdomen was closed. The operative diagnosis was "acute serositis and subserositis of the peritoneum, of unknown etiology." Histologic examination of the appendix was reported as showing "subacute appendicitis," but it was the opinion of the operator (E. L. E.) that the appendix was merely secondarily involved in the general peritoneal inflammatory reaction, and was not the primary focus from which the peritonitis originated.

Postoperatively the patient ran a stormy course. The abdominal phenomena subsided within a day or two, but the fever, tachycardia and dyspnea continued. On May 2, 1928, a parotid infection developed which was drained through Stenson's duct by massage of the gland. On May 5, 1928, the patient appeared to be improving, but on May 7 she developed acute knifelike precordial pain, a marked pericardial friction rub and impairment of the percussion note, tubular breathing and râles at the base of the left lung. There was no cough. On May 9, 1928, she was transferred to the medical service. Blood count at that time showed erythrocytes, 4,000,000; leukocytes, 13,500; hemoglobin, 64 per cent (Sahli); and a differential count of: neutrophils, 66; lymphocytes, 30; large mononuclears, 4 per cent. Urine analysis showed findings identical with those previously reported. Blood urea nitrogen was 11 mg. per cent. Fasting blood sugar was 120 mg. per cent. Roentgenographic examination of the chest suggested the possibility of pericardial effusion, but pleural effusion was not ruled out. A blood culture was negative. The patient's condition improved very slightly during the next two weeks; then more definite signs suggesting pericardial effusion were elicited. On May 26 a needle was inserted in the sixth left interspace in the midaxillary line, and directed posteriorly. About 300 cc. of serosanguinous fluid were removed. It

was thought that a pericardial rather than a pleural collection had been withdrawn, because of the position of the needle, because impulses were transmitted to it from the heart and because the area of cardiac dullness was smaller after the tap. Following the paracentesis the patient's condition improved temporarily, but on June 5, an abrupt rise of temperature occurred and she developed pulmonary signs suggesting the presence of bronchopneumonia. Congestive failure supervened with hepatic engorgement, increased dyspnea and vomiting. Death occurred on June 8, 1928; permission for a necropsy was not granted. Cultures from the peritoneum at operation and subsequent ones obtained from the pericardial effusion were sterile.

Review of the Literature. The literature contains accounts of a number of cases of presumable "rheumatic peritonitis," the majority of which have been reported by the French. These cases all have the following points in common: (1) Signs and symptoms of peritoneal irritation; (2) a close association of these phenomena with attacks of acute rheumatic fever. A number of French clinicians have accepted the existence of "rheumatic peritonitis" as an established fact. There has been a reasonable doubt, however, in the minds of many careful observers as to whether the available circumstantial evidence was sufficient to justify a final acceptance of peritoneal rheumatism as a proven entity.

Andral*[2] is reputed to have been the first to call attention to this syndrome. In 1839 he reported the case of a rheumatic patient, whose joint symptoms disappeared, and were followed by a fatal peritonitis with a hemorrhagic exudate. In 1840 Huxam[3] called attention to the abdominal phenomena of rheumatism. He noted that rheumatic fever could begin with abdominal pain, vomiting and diarrhea, and remarked upon the alternation between joint and abdominal symptoms, that is, when the one appeared the other subsided, and *vice versa*. Chauffard[2] (1863) reported a case in which a "primary peritonitis" was followed by articular manifestations. The outcome was favorable. Dyonys de Sejour[2] (1866) reported a case of articular rheumatism, in which an attack of peritonitis was preceded and followed by polyarthritis. The patient recovered. Desplats[2] (1873) described the case of a patient with acute rheumatic fever who developed peritonitis and died in seven days. Necropsy showed a generalized peritonitis, most marked toward the mesentery and the lesser peritoneal sac. Blanckey[2] (1884) reported a case of rheumatic polyarthritis, during which there appeared successively "endopericarditis," double pleurisy, general peritonitis of three days' duration and an "encephalopathy" which killed the patient six days later. There was no necropsy. Vivant[2] (1884) reported the case of a patient with an old mitral endocarditis, who developed polyarthritis, endocarditis and terminal

* A number of the older references to rheumatic peritonitis are contained in the Dictionnaire Encyclopédique des Sciences Medicales,[2] a source from which material has been drawn rather freely.

serofibrinous peritonitis. Packard[4] (1888) reported the case of a boy with a rheumatic history who became suddenly acutely ill with severe pain in the right lower quadrant, diarrhea, vomiting, fever (102° F.) and tachycardia (120 beats per minute). Subsequently marked generalized rigidity of the abdominal muscles and exquisite tenderness developed, and the patient presented the characteristic picture of a severe fulminating peritonitis. After six days polyarthritis appeared, and the abdominal phenomena vanished in twenty-four hours. The polyarthritis yielded to salicylates, and the patient was well enough to leave his room in a few days. Greene[5] (1889) reported the case of a boy with acute articular rheumatism, in whom the joint phenomena subsided simultaneously with the appearance of acute pain in the region of the stomach accompanied by repeated vomiting. "Invasion of the joints was followed by amelioration of the gastric symptoms and *vice versa*." After developing bilateral purulent parotitis the patient made a recovery which was "tardy in the extreme." An organic cardiac lesion developed during the course of his illness. Yeo[6] (1894) reported the case of a girl, aged eighteen years, with a past rheumatic history and recent phenomena suggesting subacute rheumatic activity. The patient developed fever, vomiting and constipation, together with pain, tenderness and rigidity in the right iliac fossa. At one time during the course of the peritonitis the author reports "We were able to make out distinctly, on gently pressing the abdominal wall with the hand horizontally over the subjacent parts, a palpable creaking friction." Polyarthritis appeared ten days after the onset. Both the abdominal and joint phenomena subsided in an astonishing fashion under adequate salicylate therapy. The author's final comment is: "Extremely rare though the occurrence is, there can be no doubt that this was a case of rheumatic perityphlitis." Brazil[7] (1895) reported 2 cases with pain and tenderness in the region of McBurney's point, and vomiting followed in a day or two by joint pains. Neither patient was operated upon. Both were cured by salicylates. Pribram[8] (1899) gave a résumé of the following 2 cases which we were unable to find elsewhere in the literature. Fuller's case was that of a girl, aged eighteen years, who developed successively polyarthritis, endocarditis, pericarditis, right-sided pleurisy, left-sided pneumonia and peritonitis. Death finally occurred from fresh pneumonia. Necropsy showed recent pericarditis, endocarditis, a serolymphatic pleural exudate and lung hepatization. There were bands of lymph and a turbid serum in the peritoneum. Marmonier's patient, a woman, aged forty-six years, had previously had two attacks of rheumatism with cardiac damage. During her third attack the joint phenomena ameliorated on the sixth day, and she developed sudden severe hypogastric pain and meteorism. The abdominal phenomena subsided in five days and pneumonia developed. The patient finally recovered. Throughout

the entire illness new joints were being continually affected. The polyarthritis disappeared simultaneously with the pneumonia and peritonitis. Küttner[9] (1906) collected a fairly large bibliography on the subject of rheumatic peritonitis, and, in addition, was the first to report a case in which the peritoneum was inspected at a surgical operation during the course of the peritonitis. A patient, aged twenty-four years, with a past rheumatic history and an endocardial lesion, developed severe pain in the ileocecal region, fever (39° C.) and tachycardia. There was no vomiting. The urine was negative. There was a leukocytosis of 13,000. Rectal examination was negative. Operation was performed with the tentative diagnosis of "appendiceal perityphlitis," with rupture and general peritonitis. No exudate in the peritoneal cavity, nor trace of peritonitis were found. The cecum and appendix were normal. Two days later the abdominal phenomena subsided, and a typical attack of rheumatic polyarthritis developed and ran its course. The appendix was histologically normal. Küttner reported a second case in a boy, aged ten years, who had a rheumatic history and evidence of past endocarditis. The patient developed sudden, severe pain and tenderness in the right lower quadrant with fever and constipation, but no vomiting. Two days later polyarthritis appeared. Operation was not performed. Tricot[10] (1908) reported the case of a soldier, aged twenty-one years, who developed diffuse abdominal pain and tenderness, with vomiting, fever and tachycardia. The symptoms became progressively more marked during eleven days of observation, and since localization to the right side of the abdomen occurred, operation for appendicitis was performed. The operative findings were a lemon-colored fluid in the abdominal cavity and peritoneal injection. Careful exploration revealed no evident cause for these findings. After operation there was a marked relief of pain, but the general febrile reaction continued. Four days postoperatively polyarthritis appeared. The patient's abdominal and joint symptoms subsided rapidly under salicylate medication. At one time, due to a gastric upset, salicylates were temporarily discontinued. This was immediately followed by a recurrence of fever, joint pains and abdominal symptoms. On resumption of salicylate therapy, all these manifestations once more rapidly disappeared. During the course of the illness a systolic apical murmur appeared. Several weeks after discharge there was a recurrence of abdominal symptoms identical with those present in the first attack, followed in two days by polyarthritis. This episode was likewise rapidly terminated by salicylate medication. Rolly[11] (1920) described 2 cases of peritonitis among 3620 cases of acute rheumatic fever. One was diagnosed clinically, the other, postmortem. He remarks that an existing involvement of serous surfaces often is not suspected clinically. Poynton[12] (1925) stated: "In fatal cases of rheumatic fever a chronic peritonitis may be

found around the liver and spleen. On one occasion the writer heard a loud peritoneal friction during life, and in another there was complaint of abdominal pain over the upper segment of the abdomen, where peritonitis was demonstrated after death." Poynton also states that he has never found acute changes in the appendix in fatal cases of rheumatic fever. In 1926 Graham and Paul,[13] while making a postmortem study of a series of 18 fatal cases of rheumatic fever, noted the occasional presence in the abdominal cavity of a fluid exhibiting the characteristics of an exudate.

Later, in 1930, Paul[14] reported the case of a patient who had rheumatic polyarthritis, endocarditis, pericarditis, pleurisy and "pain in the side." At necropsy a *serofibrinous peritonitis* was found which was confined to the upper abdomen in the region of the liver and spleen. *The peritoneal lesion closely resembled, both grossly and histologically, coëxistent pleural and pericardial lesions which were of a typical rheumatic nature. There were histologic rheumatic lesions in the underlying hepatic and diaphragmatic tissues.* Cultures from the pleural, pericardial and peritoneal surfaces were sterile. Bezançon and Weil[15] (1926) described the case of a man, aged twenty-six years, who developed fever and severe right lower quadrant pain, which was considered appendiceal in origin. Six days after onset the abdominal pain disappeared and polyarthritis developed. Five days later the fever subsided. Before discharge a systolic mitral murmur appeared. Grenet and Delalande[16] (1928) reported 2 cases in which diarrhea preceded polyarthritis, the so-called "prearthropathic diarrhea." They also described the case of a child, aged seven years, who developed constipation, abdominal pain and meteorism. The diagnosis of appendicitis was made, but operation was delayed. Eight days later the abdominal pain subsided and polyarthritis began. Salicylates effected a cure. Pilod and Meerseman[17] (1928) reported the case of a patient with tonsillitis who developed a high fever, polyarthritis and precordial constriction. During this episode severe generalized abdominal pain appeared without vomiting or constipation. Subsequently the pain localized near McBurney's point, and tenderness and rigidity developed in that region. The polyarthritis subsided. Surgical intervention was undertaken on the diagnosis of "ruptured appendicitis and general peritonitis." A "turgescent appendix and mild peritoneal congestion" were found. The appendiceal changes were not considered adequate to explain the symptoms. Appendectomy was performed and the wound was closed without drainage. Postoperatively the abdominal phenomena subsided slowly, and polyarthritis, pericarditis and right-sided pleurisy developed. The administration of salicylates was followed by a fairly rapid improvement. During the course of the illness an aortic diastolic murmur developed.

Bernard[18] (1928) reported the case of a soldier, aged twenty-one

years, with tonsillitis, who developed generalized abdominal pain and tenderness, distention, constipation, fever (39° C.) and leukocytosis (20,000). There was neither nausea nor vomiting. Severe left lumbar pain and tenderness gave rise to a suspicion of perinephric abscess. Rectal tenderness was present. The heart and lungs were normal. After several days of palliation the patient was subjected to an abdominal section. A *clear serum* was found in the abdominal cavity. The appendix was long, applied to the cecum by fragile strands, and was macroscopically healthy, but nevertheless removed. The *subperitoneal cellular tissue showed an infiltration* extending the whole length of the "right laterocolic gutter." The abdomen was closed without drainage. A left lumbar incision showed no pus in the perinephric area. Postoperatively the abdominal phenomena and fever continued for seven days. Then polyarthritis appeared. The abdominal and joint symptoms cleared up under salicylates. The operative findings in this case were very much like those in our patient.

Costedoat[19] (1929) described the case of a girl, aged twenty years, with a past history of frequent attacks of tonsillitis, who developed sudden severe generalized abdominal pain, more marked in the right upper quadrant. An appendectomy was done during afebrile period. The appendix was congested, but neither swollen, perforated nor surrounded by adhesions. Postoperatively the abdominal phenomena subsided, but polyarthritis and a systolic apical murmur appeared. Salicylates brought the episode to an end.

Worms[20] (1930) described 3 cases of the "peritoneal syndrome in rheumatic fever." The first was that of a young soldier with tonsillitis, who developed sudden severe abdominal pain and tenderness localizing in the right lower quadrant, fever (39° C.) tachycardia (120 beats per minute) and vomiting. Operation for appendicitis was performed. A lemon-colored fluid was found in the abdominal cavity. There were no granulations on the peritoneal surfaces, but the serosa was somewhat injected. The appendix was normal macroscopically and microscopically. After operation the abdominal symptoms subsided, but the temperature remained inexplicably elevated for several days. Then polyarthritis developed, which "clarified the diagnosis," and yielded to salicylates. The second case was that of a young soldier who had a past history of tonsillitis and rheumatic fever. Severe infra-umbilical pain, distention, rigidity and epigastric tenderness developed. There was vomiting, fever and tachycardia. Operation disclosed nothing in the abdomen to account for the symptoms. The gall bladder, stomach, duodenum and appendix were pronounced normal. The author, however, "was struck with the congested state of the peritoneum without being able to discover its cause." Three days after operation the appearance of polyarthritis and a systolic mitral murmur "showed the rheumatic nature of the malady." The symptoms

cleared up under salicylate medication. The third case also occurred in a young soldier with a rheumatic history. During a bout of mild polyarthritis he developed a sudden pain, like a pistol shot, in the right flank, with vomiting, constipation and delirium. He was hospitalized four days later with severe abdominal pain, boardlike rigidity, vomiting and fever (40.4° C.) and tachycardia. At operation the entire peritoneal cavity was explored. Nothing was found to explain the abdominal phenomena. The next day polyarthritis developed. Salicylate medication cleared up both the joint and the abdominal symptoms within five days. In the discussion of the paper by Worms, Sauvé described the case of a girl, aged fourteen years, who developed symptoms suggesting appendicitis during an attack of tonsillitis. Operation was delayed and, thereafter, "endopericarditis" appeared.

Recently Geissinger[21] reported the case of a boy, aged five years, with otitis media, who developed severe generalized abdominal pain, vomiting, constipation, fever (101° F.), tachycardia and leukocytosis. The heart and lungs were negative. Abdominal distention and boardlike rigidity developed. Tenderness was thought to be slightly greater over the appendix than elsewhere. Operation disclosed an appendix which was normal both grossly and histologically. Extensive exploration was not made, but nothing was found in the immediate field of operation to account for the symptoms. Postoperatively the abdominal phenomena subsided, but the fever persisted. Four days later polyarthritis developed, and ten days later a pericardial friction appeared. Hyman[22] reported a case of a girl, aged six years, who, during the course of a typical attack of rheumatic fever, twice experienced bouts of right lower quadrant pain, with exquisite tenderness over McBurney's point, suggesting acute appendicitis. Operation was not performed. The author stated that subsequently he had seen 4 similar cases. One of the 4 had been operated upon, and a "subacutely inflamed appendix removed."

Several supposed cases of rheumatic peritonitis have been omitted from this review, because adequate evidence of the relation between the abdominal phenomena and rheumatic fever seemed lacking. Desclaux,[2] Bauer,[23] Lyman,[24] Grenet,[25] Dory[26] and Burke[27] have contributed articles on abdominal rheumatism, which will not be reviewed at this time. Several other references appear in the literature, but they are not included, since access was not obtained to the original documents nor to a satisfactory résumé of them.

Discussion. The foregoing review of the literature indicates the type of evidence upon which one might base a belief in the existence of rheumatic peritonitis. Many of the case reports are unconvincing. In some of the cases there may have been no true peritoneal lesion.[9,20,21] (On the other hand, a localized area of peritonitis might have been overlooked in these cases.) The abdominal physi-

cal signs might be explained as being due to any one of several other causes: (1) In certain cases they might have been due to rheumatic involvement of the abdominal muscles, analogous to torticollis, lumbago and "growing pains."[21,28] (2) In others, intra-abdominal lymphadenitis or inflammation of the lymphoid tissue in the appendix (the "abdominal tonsil") might explain the findings.[7,19,22] (3) The pain, in some instances, might have been referred from the pericardium, pleura, diaphragm or spine.

The existence of a true peritoneal lesion in certain cases, however, is supported by the following observations: (1) A peritoneal friction rub was noted in 2 cases.[6,12] (2) A definite subperitoneal edema was noted at operation in 2 cases ([18] and our case), and injection of the peritoneum together with an exudate was observed in 3 others.[17,20] (3) There can be no doubt about the existence of a peritoneal lesion in the cases examined postmortem by Paul,[14] Poynton[12] and several others.

Granting, therefore, the presence of a peritonitis in some of these cases, one must not lose sight of the fact that the etiology of this lesion may not have been rheumatic. In certain instances a non-rheumatic abdominal episode might merely have served to activate a smouldering rheumatism. In some of the older cases the peritonitis may have been caused by pyogenic organisms, which could have been recognized if modern bacteriologic methods had been available. Moreover, in some of the cases which occurred in adult females there is the theoretical possibility of explaining the clinical picture on the basis of gonococcal peritonitis and arthritis, rather than rheumatic fever. There is a considerable amount of circumstantial evidence, however, in favor of a rheumatic etiology for some of these peritoneal lesions. This evidence might be summed up as follows:

1. The remarkably *close clinical association* between the peritoneal lesions and the rheumatic phenomena suggests a common etiology.

2. There is a striking *clinical similarity* among many of the reported cases. The diagnosis of appendicitis has often been made, but the signs and symptoms have frequently been atypical of that condition. The abdominal phenomena have usually been diffuse from the very beginning, and definite localization in the appendiceal area has often been absent.

3. The *clinical course* has generally differed from that observed in other known types of peritonitis, in that the abdominal phenomena have often subsided with astonishing rapidity. This has usually occurred in the face of a continuation of the fever, and general reaction, and suggests that the peritonitis was merely one manifestation of a more generalized morbid process (rheumatic fever).

4. The peritoneal *lesions observed at operation* have been unexpected, often inadequate to explain the abdominal signs and symptoms and the severe general reaction, and inexplicable on the basis

of any other known etiology except rheumatism. This is especially true in the two cases in which peritoneal and subperitoneal edema and infiltration were found.

5. The peritoneal *lesions observed at necropsy* have been of an unusual type. In Paul's case[14] the peritonitis closely resembled, both grossly and histologically, coëxistent pleural and pericardial lesions which were of a typical rheumatic nature. Moreover, there were histological rheumatic lesions in the subjacent tissues.

6. *Cultures* taken from peritoneal lesions in at least two instances ([14] and our case) were negative.

The evidence, therefore, makes it difficult to account for these peritoneal lesions, except on a rheumatic basis, and, in addition, gives a certain amount of support to the possibility of a rheumatic etiology. Only one case of "rheumatic peritonitis" has come to our attention in which microscopic examination of the intraäbdominal tissues has been reported.[14] Unfortunately, therefore, the most important single link (histologic confirmation) in the chain of evidence necessary to establish the rheumatic etiology of these peritoneal lesions is, at present, the weakest. It is to be hoped that histologic evidence will accumulate more rapidly if the profession as a whole becomes aware of the possible existence of rheumatic peritonitis, and if sections of the peritoneum and subperitoneal tissues are taken for microscopic study from suspected cases when they appear at the operating table or at necropsy.

The wisdom of describing the clinical picture, produced by a lesion whose existence is doubtful, might be questioned. Nevertheless, since many of the reported cases of "rheumatic peritonitis" have possessed certain points of similarity, it seems justifiable to attempt a summary of the clinical phenomena: The patient is usually young. As a rule, there is a past rheumatic history. Signs of rheumatic valvular damage are often elicited in the cardiac examination. Abdominal pain and signs of peritoneal irritation appear during the course of, or sometimes prior to, the onset of an attack of acute rheumatic fever. There is usually a severe general reaction, high fever and a leukocytosis (often over 20,000). The signs and symptoms frequently suggest appendicitis with rupture and peritonitis, but the abdominal phenomena are apt to be more diffuse from the very onset than is usually the case in appendicitis, and localization in the right lower quadrant is less apt to occur. If the patient is operated upon, one may find clear fluid in the abdomen and hyperemia, edema and infiltration of the peritoneum and subperitoneal tissues, without evident intraäbdominal cause. A striking feature of many of these cases has been the rapid and unexpected subsidence of the abdominal signs and symptoms in the face of a continuation of the fever and general phenomena. The presence of diarrhea and the absence of vomiting have been

noted by some writers, but they are not constant features. Their presence or absence may be dependent upon the location of the peritoneal lesion. The alternation of peritoneal and joint phenomena is probably not a strict necessity, but has been frequently mentioned in the literature as an important point in the clinical picture. Salicylates have been said to be almost as specific for the peritoneal as for the arthritic pain. We have had no experience to corroborate nor to deny this statement.

There are two facts which make it possible that rheumatic peritonitis may occur more often than we have supposed heretofore: (1) Mild abdominal pain is a very frequent symptom in rheumatic children. So much so, that those who see a large number of cases of juvenile rheumatism[28,29] consider it to be a typical rheumatic phenomenon and a sign of rheumatic activity. (Pearson[29] has carefully studied and accurately described this type of pain.) It is conceivable that this type of pain may be due to a localized area of mild rheumatic peritonitis. (2) Graham and Paul,[13] in reporting a postmortem study of 18 fatal cases of acute rheumatic fever, stated: "We occasionally noted in the abdominal cavity the presence of a fluid exhibiting the characteristics of an exudate." In none of these cases had an antemortem diagnosis of intraäbdominal inflammation been recorded. It may be, therefore, that rheumatic peritonitis often occurs in a mild form without producing striking symptoms.[11]

It seems advisable, in concluding this discussion, to call attention to certain fulminating cases of appendicitis which occur in close association with tonsillitis and pharyngitis. We have seen several of these, in which delay of surgical intervention might well have been of serious consequence. It is not our intention to counsel such delay. When confronted with a case of possible appendicitis in a patient with a throat infection, it is probably wise to err on the safer side, namely, to open the abdomen. The existence, and especially the diagnosis of "rheumatic peritonitis," is as yet too uncertain to justify one in taking any other position.

Summary. 1. A patient with a past rheumatic history and a well-marked rheumatic cardiac lesion developed lower abdominal pain, diarrhea and signs of peritoneal irritation. She was operated upon on the supposition that a ruptured appendix and pelvic peritonitis were present. Operation disclosed an abundance of clear fluid in the peritoneal cavity and an acute serositis and subserositis of the peritoneum of unknown etiology. No suppurative focus was found in the abdomen, despite careful exploration. Within a few days after operation the abdominal signs and symptoms largely subsided, but the fever and general phenomena continued unabated. Nine days after operation acute pericarditis developed, and after a stormy course of typical cardiac rheumatism of six weeks' duration the patient died. No signs of Neisserian

infection had been noted at any time. Cultures from the peritoneum and subsequent ones obtained from a pericardial effusion were sterile.

2. The literature contains a considerable number of reports of cases of presumable "rheumatic peritonitis." In a certain number of these the clinical, operative and necropsy findings establish beyond question the presence of a peritoneal lesion.

3. There is no proof that these peritoneal lesions are rheumatic in etiology, but the following observations are pertinent: (1) The close clinical association of the peritonitis and the rheumatic fever suggests a common etiology; (2) the peritoneal lesions do not resemble in appearance nor in clinical course any other known type of peritonitis; (3) in one fatal case of acute rheumatic fever a serofibrinous peritonitis was found, which resembled grossly and histologically coëxistent, typically rheumatic lesions in the pleura and pericardium.

4. It seems worth while, therefore, to bear in mind the possibility of rheumatic peritonitis in the differential diagnosis of abdominal pain when it occurs in a patient with signs of present or past rheumatic fever.

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A TOOTH IN THE PLEURAL CAVITY.

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The literature contains occasional references to the finding of foreign bodies in the pleural cavity, most of which entered through artificial openings in the chest wall (injuries, operative precedures, and so forth). We were able to trace and verify only 10 reports of foreign bodies, which, having been inhaled, passed through the lungs and entered the pleural cavity.

In Carrière's[1] case an inhaled straw appeared eighteen days later in an abscess between the seventh and eighth ribs. In Bally's[2] case, an ear of barley came out, under similar circumstances, after four and a half months. Desgranges[3] reports the appearance of an inhaled grass through an abscess in the right kidney region six weeks after the accident. Herbert Mayo[4] found, at an autopsy, an ear of grain in a large abscess cavity involving the right lung and liver. The ear was inhaled by the patient, but the report does not state when the accident happened. Carpenter[5] reports a detailed clinical history and autopsy findings in a man who, at the age of twenty-two years, inhaled or swallowed a set of four artificial teeth during a spell of coughing. No further discomfort resulted. Thirteen years later he developed a pain in the chest and examination

FIG. 1.—A drawing of the diaphragmatic surface of the lower lobe of left lung showing the tooth as it was found at autopsy.

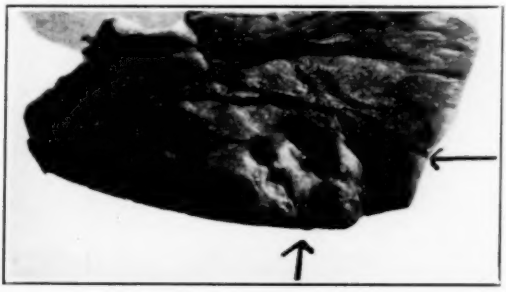

FIG. 2.—A photograph showing the five depressions in the lung after the tooth was removed.

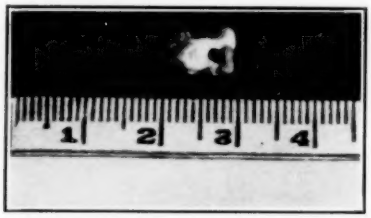

FIG. 3.—A photograph of the tooth showing the cusps on its upper surface.

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showed pleuritis on the right side. The patient died without relief after a long illness. At autopsy a piece of ivory consisting of four artificial teeth was found in the pleural cavity. A fistulous opening on the outer lateral surface of the lung led into an abscess cavity. The esophagus showed no evidence of scars. In Marrow's[6] case a grass came out through an abscess in the chest wall two months after it was inhaled.

In more recent times Van Leggelo,[7] Grunert,[8] Strauven,[9] and Tanasesco,[10] reported similar courses of inhaled ears of rye and barley, which entered the pleural cavity. All cases had, in common, an infectious process leading to more or less pronounced signs of sickness.

Case Report. The patient, a woman, aged thirty-three years, unmarried, had been under medical care for rheumatic heart disease since she was fifteen years of age. She was first admitted to the hospital in July, 1925, and left improved after a month's stay.

The last admission was in February, 1929. The clinical diagnosis was subacute bacterial endocarditis on the background of a rheumatic heart disease, mitral stenosis and regurgitation, aortic valvulitis and cardiac hypertrophy. The patient did not improve, showed signs of emboli in various parts of the body and expired on March 10, 1929.

At *autopsy* the heart showed a vegetative endocarditis of the mitral valve, chronic endocarditis of the mitral, aortic, and tricuspid valves, with resulting stenosis and insufficiency of the mitral and aortic ostia, and stenosis of the tricuspid ostium, fibrosis of the heart muscle, hypertrophy of the walls and dilatation of the chambers. In the spleen and kidneys numerous infarcts were found. A softened area was present in the right internal capsule of the brain. Chronic passive congestion was present in both lungs.

The left lung was densely adherent to the chest wall along its lateral surface, but its diaphragmatic surface was free, and attached to it there was a hard, discolored body having the shape and general appearance of the crown of a tooth (Fig. 1). It was easily dislodged, leaving in the pleura five depressions, corresponding to the five prominences on its surface (Fig. 2). It (Fig. 3) measured 8 mm. in length, 7 mm. in width, and its thickness was 2 mm. without the cusplike projections, and 4 to 6 mm. with them. The flat base was brown, the other surfaces gray. The consistency was firm but elastic.

The *histologic* examination of this peculiar body found in the pleural cavity revealed the presence of enamel and dentin, and proved it to be indeed a tooth, which was later identified with the help of Dr. A. Hopewell-Smith, Professor of Dental Pathology at the School of Dentistry of the University of Pennsylvania, as the crown of a second mandibular deciduous molar, the root of which had been absorbed.

A careful examination of the lung failed to reveal any evidence of infection, old or recent, with the exception of the already mentioned dense pleural adhesions.

Comment. As it is assumed that the deciduous teeth are shed not later than at the age of twelve or thirteen years, about nineteen to twenty years had elapsed since this tooth, being accidentally inhaled into the left bronchus, began its migration into the pleural cavity. It is possible that the point of entrance was not at the place

where it was found at autopsy. The adhesions along the lateral aspect of the lung may point to a perforation higher up with a subsequent inflammation due to irritation. The tooth itself sank to the lowest point, and there it was found at autopsy. The long time which intervened between the inhalation of the tooth and the patient's death may explain the absence of any evidence of the destructive path which the tooth had traveled.

The striking feature of this case is the absence of any detectable pathologic changes in the lung, with the exception of the pleural adhesions. Also of interest is the very long time during which the tooth was in this unusual location without occasioning symptoms.

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HYPOGLYCEMIA WITH COMA IN A CASE OF PRIMARY CARCINOMA OF THE LIVER.

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Hypoglycemia and hyperinsulinism, since first described and named by Harris, due to the widespread employment of blood-sugar tests and our better understanding of carbohydrate metabolism, has repeatedly been reported. Recently, Allan, Boeck and Judd have discussed the surgical treatment of certain cases of this condition. A definite pathologic basis for hyperinsulinism was demonstrated in the case seen at the Mayo Clinic in 1926, namely, the overproduction of insulin due to carcinoma of the pancreas originating in the islands of Langerhans. Similar cases have been reported by

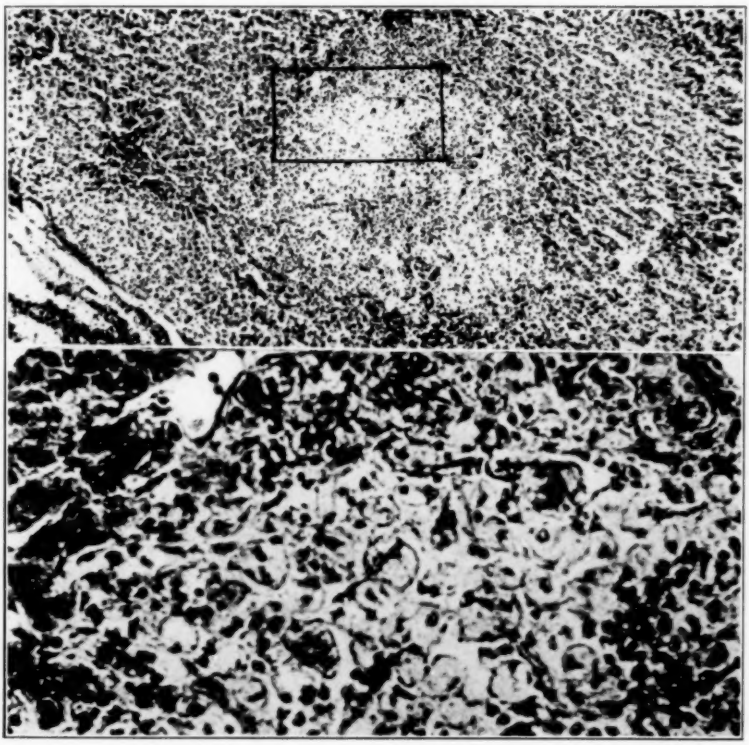

FIG. 1.—An area of parenchymatous degeneration and necrosis, showing a central area of pyknotic nuclei and an intermediate zone where the cytoplasm has mostly disappeared. *A*, low power; *B*, high power of the area enclosed in the rectangle.

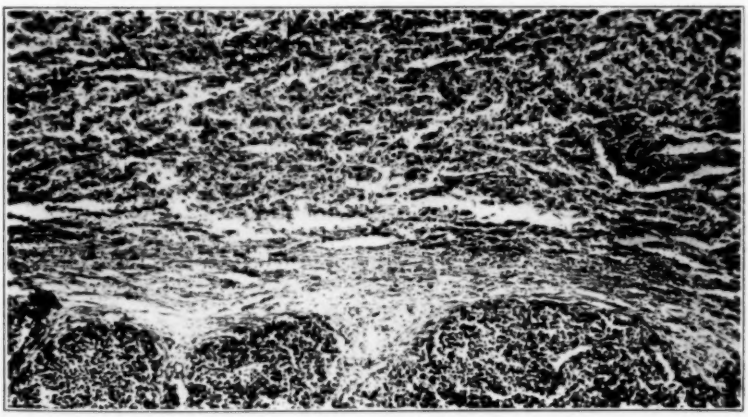

FIG. 2.—An encapsulated carcinomatous area at the bottom, showing the undifferentiated type of tumor cells. In the liver tissue of the upper half can be found a few accumulations of small round cells (see arrow).

McClenahan and Norris, by Thalhimer and Murphy and by Howland, Campbell, Maltby and Robinson. Allan reported 2 cases in 1929. A case of Hartmann has likewise been believed to be hyperinsulinism. The Finneys reported still another case treated by operation. A severe case of hepatogenic hypoglycemia without other gross evidence of hepatic dysfunction was studied by Nadler and Wolfer. To this we may add the following:

Report of Case. M. A., a colored male, aged forty-two years, was admitted to the Episcopal Hospital, December 22, 1926.

Family History. Married four years. Wife living and well (one miscarriage); no history of familial diseases.

Past History. Malaria at ten years; influenza in 1918; chancre followed by antiluetic treatment several years ago, also gonorrheal infection.

Present Illness. Pain in the epigastrium.

About six weeks previous to entering the hospital he was struck a glancing blow in the abdomen by the tail board of his wagon, while dumping a load of ashes. He had severe pain for about thirty minutes, at the end of which time he went home. The following day he had much pain and misery, and reported to a local hospital where Roentgen ray is said to have shown a broken rib. However, the abdominal pain continued, chiefly in the epigastrium. His appetite was fair, and he ate small meals rather often, as he found that eating would sometimes give him relief from pain. If he did not eat he would get "dizzy spells and would talk simple and go out of his head" for several minutes at a time. He claimed to know what was being done during the spell, but that he was unable to control himself or to speak correctly. When the spell passed off he would eat something and feel better. He found that the juice from canned peaches gave relief. He had no vomiting, no belching of gas, but was nauseated. He gave no history of stomach trouble previous to the injury. He drank four or five glasses of water daily, and had nocturia two or three times nightly. There was no urgency, burning or other urinary symptoms. He had no headache and no symptoms referable to the cardiorespiratory systems.

He had continued to lose weight, about 50 pounds in all, and the spells became more frequent and more severe, compelling him to seek hospital care.

Physical Examination. A large, fairly well nourished, middle-aged colored male, weighing about 225 pounds.

Head: No abnormalities.

Ears: No discharge or tenderness.

Eyes: Pupils round and equal and react sluggishly to light and accommodation. No extraocular palsies or nystagmus. No scleral jaundice.

Nose: No discharges or obstructions.

Mouth: Teeth in fair condition. Tongue slightly coated, moist and protrudes in the midline without tremors.

Neck: No adenopathy. No thyroid enlargement.

Chest: Expansion fair and equal.

Lungs: Resonant throughout. An occasional râle heard at the left base. No dullness to percussion.

Heart: Not enlarged. No murmurs, no shocks nor thrills.

Abdomen: There was a slight bulging of the epigastrium rising sharply at the lower costal border. The liver extended down to within 2 cm. of the umbilicus, was firm, smooth and tender over an area just above the umbilicus. There was also a mass in the left hypochondrium coming down as low as the umbilicus. This mass did not have a sharp edge or notch, and felt as if there were bowel overlying it and tied down with adhesions. Peris-

talsis was loud and active. There was well-marked distention of the lower abdomen, tympanitic, no movable dullness in the flanks and no hernia present.

Rectum: No masses; prostate not enlarged.

Extremities: Patellar reflexes present; no Babinski nor ankle clonus. No edema.

Progress. December 23, 1926: At 7 A.M. venepuncture for routine blood chemistry was done. At 9 A.M. the patient was found in coma. He was breathing quietly, like natural sleep. His skin was cool and wet with perspiration. Saliva was dribbling from his mouth and tears flowing from both eyes. Pupils were equal and moderate in size. He made no response to pressure over the supraorbital nerve. Blood pressure, 150 systolic and 85 diastolic. Pulse, 78, regular and strong. Respirations were 20, with sonorous râles due to throat mucus. The breath had no odor of a uremic nature nor of acetone. There were muscular twitchings of the upper and lower extremities, but no true convulsive movements.

The condition was serious. Oil ricini, 1 ounce, and Oil tiglii, minim. ii, were given by mouth. Thirty minutes later coma was still more profound and 40 units of insulin were given. He became still worse, respirations were more labored and he began to choke on his own tongue, so that it had to be held forward with forceps. Pupils were smaller than an hour previously. Temperature, 97.4° F.; pulse, 72; respirations, 26. At 10 A.M. we obtained a report on the blood which had been taken at 7 A.M. Blood sugar was 33 mg. per 100 cc. As soon as possible 35 cc. of 50 per cent glucose was given intravenously. Within three minutes the patient regained consciousness. Blood urea as taken at 7 A.M. was 17.8 mg.; uric acid, 2.4 mg.; creatinine, 1.4 mg. per 100 cc. blood.

At 2 P.M. the patient had two visitors and was apparently normal.

At 4 P.M. the patient was again in coma, with rapid incoördinate contractions of the muscles of all extremities. The patient voided during this coma. Forty cubic centimeters of 50 per cent glucose was given intravenously. Before the injection was completed the patient became conscious.

At 5 P.M. the patient was feeling very well and answered many questions concerning his condition.

December 24, 1926: During the past twenty-four hours the patient was given more than 2 liters of sweetened orange juice and 190 cc. of 50 per cent glucose in water and whisky. The blood sugar at 7 A.M. today was 25 mg. per 100 cc. Blood urea, 17.8 mg.

The following consultations are reported:

1. Medical: At 12.15 P.M. Dr. C. made these notes: "Liver enlarged; mass in splenic region. Believe there are adhesions, also that the bowel is involved in the adhesions of the epigastrium, as it can be palpated and gas can be heard passing along the epigastrium. Probably traumatic; advise a glucose-tolerance test. Also antiluetic treatment."

2. Surgical: At 12.30 P.M. Dr. A. reports as follows: "The liver is enlarged down to within 2.5 cm. of the umbilicus. The spleen is enlarged or there is a mass in the splenic region and the bowel can be felt slipping over something between the spleen and liver, probably a retroperitoneal mass. A nodule can be felt at about the tip of the tenth or eleventh rib, right side, and may be the tip of the costal cartilage. The liver is hard and not tender. Believe the diagnosis is malignancy or syphilis, and is an inoperable and nonsurgical case."

3. Neurologic: At 1.30 P.M. Dr. W. reports: "At the start of this examination the man was unconscious and had Cheyne-Stokes breathing or something simulating it. He was sweating profusely, tears rolled from his eyes and saliva from his mouth. A few minutes after being given

35 cc. of 50 per cent glucose intravenously he was talking and answering questions fairly well. He knew he was in a hospital, its location and the date. Examination failed to reveal any evidence of organic disease of the nervous system."

4. Ophthalmologic: Dr. G. reports: "Media clear; eyegrounds negative. Has a deepened physiologic cup in O. D. O. S. normal depth."

5. Roentgen ray: Dr. B. reports: "The outline of the sella is clearly shown and is quite large for a normal-sized skull. There is increased density and thickening around the posterior clinoid which I think is abnormal. There is no evidence of pressure, as it would be shown by erosion of the roof of the sphenoids and clinoids."

6. Laboratory reports: Sugar-tolerance test: Before glucose was given, 58 mg. per 100 cc.; one-half hour after 100 gm. glucose (orally), 102 mg. per 100 cc.; one hour after, 100 mg.; one and a half hours after, 97.5 mg.; two hours after, 72 mg.; three hours after, 50 mg.

Blood Wassermann, negative; blood CO_2, 68.1 vol. per cent; blood pH, 7.6; icterus index, 6.8; van den Bergh, negative (both direct and indirect); blood sugar, lowest reported, 25 mg. per 100 cc.; highest reported, 147 mg. per 100 cc.; blood urea, 17.8 mg. per 100 cc.; blood uric acid, 2.4; blood creatinin, 1.4; blood platelets, 600,000; blood count: hemoglobin, 56 per cent; red blood cells, 4,400,000 (no nucleated red blood cells); white blood cells, 8500; polymorphonuclears, 64 per cent; transitionals, 1 per cent; lymphocytes, 35 per cent.

Urine at no time showed sugar, acetone or diacetic acid. Specific gravity varied from 1.011 to 1.020. Acid; amber color; albumin, a faint trace; bile, a trace; casts, none.

Spinal fluid: Culture, negative in twenty-four, forty-eight and ninety-six hours; cells, 1 per c.mm.; globulin, not increased; sugar, 28.5 mg. per 100 cc. (that is, much decreased); spinal Wassermann, negative in 1.5 cc.; colloidal-gold curve, 555553100000.

December 26, 1926, to January 2, 1927: Daily carbohydrate intake ranged between 1700 and 2200 gm.

December 29, 1926: Roentgen ray of lungs shows fine mottled nodular infiltration present throughout both lungs. Appearance is that of a metastatic condition. Diaphragm shadows normal.

January 2, 1927: Patient began to vomit orange juice. Dry sucrose, chocolate, and sweetened tea and lemonade were substituted.

January 4, 1927: Having a good deal of pain over the liver area and M. S., $\frac{1}{6}$ grain, had to be given.

January 5, 1927: More pain was present over lower area, and the liver was felt to be nodular and tender; general condition became worse.

January 6, 1927: Began to refuse food.

January 7, 1927: Found dead at 5.40 A.M. (nurse reported him as sleeping quietly at 5 A.M.).

Necropsy. The significant postmortem findings were as follows:

Liver: 85 by 60 by 25 cm.; weight, 4150 gm. Nodular and filled with cancerous growths of various sizes and shapes, occupying fully three-fourths of the liver tissue. Microscopic: Foci of parenchymatous degeneration, with scattered bile, pigment and interstitial changes. These were circumscribed foci, occupying less than one-tenth of a low-power field, in which the liver cells had either entirely disappeared or lost varying quantities of cytoplasm with pyknosis of nuclei. (Fig. 1.) In these, but little inflammatory reaction was apparent. More numerous were smaller collections of small round cells (Fig. 2.) The medullary carcinoma of the liver (primary) occurred in large alveoli of medium sized, undifferentiated cells, completely obliterating the normal liver structure.

Pancreas: 55 by 7.5 by 5 cm.; weight, 100 gm.; reddish-gray color; normal size and appearance. Microscopic: No carcinoma found. The few islands of Langerhans seen appeared normal.

Stomach: Showed no evidence of tumor or ulcers. The mucous membrane was pale.

Lungs: Passive congestion and metastatic medullary carcinoma.

Intestines: Chronic enteritis.

Kidneys: Passive congestion; parenchymatous degeneration; slight increase of interstitial tissue.

Spleen: 31 by 20 by 8 cm.; weight, 175 gm.; congested and shows fibrous thickening of the trabeculæ.

Adrenals were normal.

Prostate: General fibrosis.

All other organs examined showed the grossly normal findings.

The interpretation of this case is difficult. The possibility must be considered of its being a clinical example of what happens experimentally when an animal's liver is removed or extensively injured. It is very similar to the case which was studied and reported by Nadler and Wolfer. Like their case, it shows a normal sella turcica, normal adrenals, normal blood pressure, normal pancreas and normal liver function, as shown by the icterus index, van den Bergh tests, and blood urea, but a severe hypoglycemia and the presence of an extensive primary carcinoma of the liver.

The liver in this case weighed 4150 gm. which is about two and a half times the size of a normal liver. Considering that about three-fourths of this was cancer tissue, it would still leave us 1000 gm. of liver tissue. Estimating that less than one-half of this was involved in the parenchymatous degeneration (though the involvement was actively much less than one-half), we would still have 500 gm. of functioning liver tissue. Mann has shown in dogs that he could remove all but 15 per cent of the liver with only slight changes in blood-sugar levels; 15 per cent of an average normal liver for this case would be about 333 gm., which still leaves us a good margin of safety as functioning liver tissue.

It will be noted that from December 26 to January 2 an accurate account of the daily carbohydrate intake shows the consumption of from 1700 to 2200 gm. The greater part of this was in the form of sweetened fruit juices. During this period the amount of urine was not noticeably increased and was sugar-free. The respiratory rate remained normal. The body weight was not checked nor a basal metabolism test done, but it is almost inconceivable for an individual lying quietly in bed to metabolize 2000 gm. of carbohydrate daily without more clinical manifestations (hyperglycemia, glycosuria, etc.) than was shown by this patient. The blood-sugar tests during this period show 62.5 mg. on December 28, 126 mg. on December 31 and 124 mg. on January 5. This tremendous intake of sugar was not unduly increasing the blood glucose, while at the same time it was necessary to his comfort, for as soon as the intake

was reduced hypoglycemic coma and death followed. The absence of hyperglycemia and glycosuria on such an intake is against the hepatogenic theory, and is a point in favor of hyperinsulinism. However, the character of the blood-sugar curve after 100 gm. glucose is contrary to what would be expected in hyperinsulinism. On the other hand, it is difficult to imagine an injury to the liver so extensive as to cause hypoglycemia and not cause other alterations in hepatic function.

The effect produced by the blow on the abdomen at the onset of symptoms cannot be determined. Did it pave the way for a more rapid growth of the cancer? Did it in any way affect the splanchnic nerves or the pancreas? Or is it only incidental?

Wilder, in his discussion of Elliott's presentation,[11] states that the case operated upon by Finney, in which no tumor was found, and in which the tail and part of the body of the pancreas was resected, has recovered. His conclusion is that there may be a hyperfunction of the islands of Langerhans in the absence of any demonstrable lesion. What possibility has such a supposition in this case where an otherwise normally functioning liver should be able, together with the muscle tissue, successfully to store sufficient glycogen to stabilize sugar metabolism? Probably the future will reveal a satisfactory explanation. The facts are that two definite cases of fatal hypoglycemia have existed in individuals having an extensive primary carcinoma of an otherwise normally functioning liver to account for it. If, as assumed in the case of carcinoma of the islands of Langerhans, there was an overproduction of insulin, an hypoglycemia, due to the tumor arising in that tissue, could there not be in these cases an overproduction of some hormone, either directly or indirectly causing the rapid metabolism of dextrose?

Conclusions. 1. A case of spontaneous hypoglycemia is reported.

2. The chief lesion is in the liver, a primary medullary carcinoma, together with foci of parenchymatous degeneration.

3. The pancreas and its islands of Langerhans, the adrenals and pituitary were apparently normal.

4. There was a complete loss of the ability to stabilize carbohydrate metabolism, in that the blood-sugar level was not spontaneously maintained at the normal height.

5. Sufficient normally appearing liver tissue was apparently remaining, so that the mechanism producing the hypoglycemia is still unknown.

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AGRANULOCYTOSIS (MALIGNANT NEUTROPENIA).

Report of Nine Cases, Two With Recovery.

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This report is based upon the observation of 9 cases diagnosed as agranulocytosis and seen between November, 1928, and April, 1930. Since Schultz's[1] original observations in 1922, of a group of cases of severe sore throat associated with marked leukopenia—("angina agranulocytica") a large and ever-increasing number of cases, totaling now about 200, has been reported. This extensive literature has been adequately reviewed by Kastlin[2] and others, and will not therefore be fully discussed here. The name at present in most general use for this condition is agranulocytosis. The term agranulocytic angina, first suggested by Schultz,[1] has been shown inadequate since many cases occur in which sore throat (angina) is absent. Schilling[3] suggested the term "malignant neutropenia" arguing rightly that agranulocytosis, strictly defined, signifies a proliferation of the cells without granules. "Sepsis agranulocytica," "mucositis necroticans agranulocytica," "angina necrotica," "malignant leukopenia with sepsis" are other terms which have been proposed. Long before Schultz's descriptions, Frank[4] reported a case of sepsis with complete lack of regenerative powers in the bone marrow, and suggested the word "panmyelophthisis." It is felt

that the term "malignant neutropenia," being sufficiently descriptive, and not too unwieldy, deserves more general use. In this clinical report, it is intended to describe the cases seen, and to discuss in some detail the differential diagnosis, laboratory data, and therapy of the disease.

Case Reports. CASE I.—Seen by one of us (W. D.) with Dr. R. W. Buck, of Boston, Mass., on November 7, 1928. This case was recently reported by Buck in the *Journal of the American Medical Association*.[5] A woman, aged forty-five years, had had "anemia" twenty years previously. In 1924 she had "lumbago." For three months before her present illness she had "grippe" and had felt somewhat weak since. In September, 1928, she complained of pain in the region of the anus; there was marked swelling and the pain increased rapidly. On October 15, 1928, hemorrhoidectomy was performed. She grew weak and pale after the operation; there was slight fever and marked loss in weight. On October 28 she was found to be quite ill and mentally dull. Temperature was 101.4° F. Throat and buccal mucosa were normal. Lungs showed an area of consolidation near the right base. The heart was enlarged, the sounds of poor quality. Examination of the rectum showed a moderate amount of foul-smelling discharge and an unhealed oval fissure. Typhoid fever, pneumonia, sepsis, meningitis, syphilis and tuberculosis were all considered in the differential diagnosis, but were soon ruled out by appropriate laboratory tests. On November 11 rectal examination showed induration in the perianal regions and a superficial ulcer. On digital examination, a crater-like ulcer, about 25 mm. in diameter, was felt on the left side of the anal canal. There was marked induration in an area extending out 3 cm. from the edges of the ulcer. There was no evident infection in the superior pelvirectal spaces, or localized infection of the perirectal or ischiorectal region. Proctoscopic examination was not done. On November 7 a bone-marrow biopsy (sternum) by one of us (W. D.) with Dr. S. Gargill showed a red marrow with nothing characteristic microscopically. On December 3, 1928, the patient died shortly after a transfusion.

Laboratory data are given in the form of a chart.

CASE I.

	Oct. 28.	Oct. 30.	Nov. 3.	Nov. 6.	Nov. 8.	Nov. 13.	Nov. 20.	Nov. 26.	Nov. 30.	Dec. 3.
Hemoglobin (Sahli)	..	..	60	62	63	64	39	27	19	17
Red blood cells (millions)	3.2	3.2	....	2.7	2.5	2.0	1.6	1.3	0.85	1.08
White blood cells	4,000	4,000	....	2,100	3,500	3,350	2,550	2,600	1,700	
Platelets	..	..	100,000							
Neutrophils	..	21	....	..	4					
Lymphocytes	..	70	....	..	80					
Monocytes	..	6	....	..	16					
Eosinophils	..	2								
Basophils	..	1								

Postmortem examination disclosed pleural and pericardial effusion, cardiac hypertrophy and dilatation, a mural thrombus in the right ventricle. The spleen was large and friable, microscopically normal. The lymph nodes were normal. Bone marrow (femur) showed moderate activity of both red and white cell elements and many megakaryocytes (acute hematopoiesis). The anal ulcer had healed.

To summarize, this was a case in which a debilitated woman, aged forty-five years, developed pain and swelling about the anus followed by ulceration and continued fever. Differential diagnosis was very difficult. Granulocytes gradually disappeared from the blood stream. During the course of a month, hemoglobin and red blood cell count gradually decreased. Bone-marrow biopsy was essentially negative. Death occurred soon after transfusion. Autopsy showed active hematopoiesis of the marrow, without evidence of existing aplasia.

CASE II.—Seen by one of us (W. D.) with Drs. A. I. Cohen and J. V. McMackin of Boston, Mass. Frank McD., a dentist, aged forty-eight years, developed, on November 14, 1928, sore throat, chill and temperature of 105° F. About twenty years previously he had had malaria, and since then had had occasional chills. For three to five years he had been dyspneic on walking a block. In the past year or two he had not felt "up to par." On the first day of his illness Dr. Cohen found an ulcerating lesion of the left tonsil, and considered it to be Vincent's infection. Smears from the ulceration were, however, negative for the spirillæ and fusiform bacilli of Vincent's angina. The temperature fluctuated, dropping to 99° F. on the second day of the illness, and rising to 102° to 103° F. thereafter. On November 18 jaundice was noted, and there was slight diarrhea. On November 19 the patient was almost moribund and slightly delirious. There was moderate jaundice. The fauces were entirely covered by a grayish-white, firmly adherent membrane, at the edge of which could be seen a deeply red, slightly edematous zone. The lymph nodes at the angle of the right jaw and in the right cervical area were moderately swollen and slightly tender. Lungs and heart showed no abnormalities; the liver and spleen could not be felt. Hemoglobin was 80 per cent (Tallqvist); red blood cell count, 4,500,000 per c.mm.; white blood cell count, 100 to 200 per c.mm. Only 5 white blood cells could be found in counting two blood-smear preparations; of these 5 cells 3 were lymphocytes and 2 were granular cells, both metamyelocytes. Blood culture showed no growth at seventy-two hours. On November 20 the patient lapsed into coma and died; autopsy was not obtained.

This then was a fulminating case occurring in a man, aged forty-eight years, with marked throat lesions, jaundice, and almost complete lack of white blood cells. Death occurred in seven days from the beginning of the illness.

CASE III.—Seen by one of us (W. D.) with Drs. H. Morrison and P. Meltzer, of Boston, Mass., at the Beth Israel Hospital, Boston. R. K., a housewife, aged fifty-nine years, became suddenly ill on February 2, 1929, with sore throat and temperature of 104° F. In October, 1928, a cholecystectomy for gall stones was done at the Peter Bent Brigham Hospital. At this time sugar was found in the urine. She had apparently had diabetes for about ten years, but it had been mild. Since the operation the patient had felt fairly well. On February 6 Dr. Meltzer found the patient very ill, unable to swallow and her speech "thick." Along the posterior pillars, and at the base of the left tonsil, extending as far as the lateral pharyngeal wall, were several areas of superficial ulceration. On February 7 the patient was admitted to the Beth Israel Hospital. She presented at this time the picture of marked sepsis, and was almost mori-

bund. She was given insulin. On February 8 she was very cyanotic and coughed a great deal. There were signs of bronchopneumonia, chiefly in the right midchest. On February 9, following marked pulmonary congestion, the patient died. Autopsy was not obtained. The laboratory data are given in the form of a chart:

CASE III.—R. K.

	Feb. 7.	Feb. 8.	Feb. 9.
Hemoglobin (Tallqvist)	85		
Red blood cells (millions)	4.1	.....	3.6
White blood cells	2,900	4,650	4,500
Neutrophils	19	25	
Mature	1	6	
"Band"	14	18	
"Young"	3		
Myelocytes	1	1	
Lymphocytes	38	26	
Small	25	13	
Large	13	13	
Monocytes	43	49	
Ordinary	41	43	
Histiocytes	2	6	
Blood sugar	0.301	0.179	
Blood nonprotein N	0.044	0.041	

To summarize: this was another fulminating case in a woman, aged fifty-nine years, who had had mild diabetes for ten years and a cholecystectomy only four months previously. Death, apparently due to bronchopneumonia, occurred in eight days after onset of illness. The white blood cell count was not extremely low; in fact it rose before death (due to the coexisting pneumonia?). There was a very marked monocytosis.

CASE IV.—Seen by one of us (W. D.) with Dr. H. Rosenfield, of Boston, Mass., at the Beth Israel Hospital, Boston. E. M., a woman, aged forty-one years, became ill with what was diagnosed as influenza in February, 1929, eight weeks before admission to the Beth Israel Hospital, on April 21, 1929. At onset of illness she had a running nose and sore throat, and was treated by a laryngologist. During this time she complained of severe headache, which persisted to the time of admission to the hospital. On April 7 her knees became somewhat stiff and painful, but not swollen. On April 14 she had high fever. She developed severe headache and became mentally confused and unable to do her work as a real estate agent. She had had two abdominal operations for pelvic inflammation, the last operation taking place in 1924, at which time the uterus, tubes and the remaining ovary had been removed. Since the last operation she had had frequent abdominal pain, often felt debilitated and would frequently have fever. Examination on April 21, 1929, showed a rather thin woman, mentally confused. There was sustained nystagmus both horizontally and vertically. The tonsils were small and no exudate or ulceration was present. The nasal septum was perforated. There was slight tenderness over the lower abdomen and in the right costovertebral area. Vaginal examination disclosed a high cervix, the uterus being absent. Rectal examination was negative. Examination of the fundus oculi was negative.

She continued to have fever of 103° to 105° F. On April 23 Kernig's sign was slightly positive bilaterally. Spinal fluid examination on this day gave negative results. On April 25 a transfusion of 500 cc. of citrated

blood was given and Roentgen ray treatment over the tibiæ was instituted. On April 26 bone marrow biopsy (sternum) showed complete absence of myelocytes and polymorphonuclear cells, although the red-cell-forming elements were normal and megakaryocytes were present. Myeloblasts were present in increased numbers. On April 29 the patient was deaf and irrational. The transfusion wound showed signs of inflammation, and a thick grayish-white membrane appeared at the edges of the wound. On April 28 respirations rose to 40 per minute; there was slight icterus, the lungs showed congestion and the abdomen was distended. On April 29 streptococci were isolated from an anaërobic blood culture. On April 30 the left arm became extremely swollen; there was evidence of thrombosis of the veins; the transfusion wound was markedly thickened and a hard white slough was present. On May 1 the patient died. Autopsy was not obtained.

The rest of the laboratory data is given in the form of a chart.

CASE IV.—E. M.

	Apr. 22.	Apr. 23.	Apr. 25.	Apr. 27.	Apr. 28.	Apr. 29.	Apr. 30.
Hemoglobin	78	..	....	....	..	80	
Red blood cells (millions)	4.5	..	....	....	..	3.8	
White blood cells	1760	1200	600	1850	800	850	400
Platelets	..	..	316,000	....	..	155,000	
Neutrophils	49	59	....	12	..	7	
Mature	..	12					
"Band"	..	39					
"Young"	..	8					
Myelocytes	..	—					
Lymphocytes	50	38	100	88	..	93	
Small							
Large							
Monocytes	1	1					

To summarize: This was an atypical case of agranulocytosis without angina in a woman, aged forty-one years, who had not felt well for years. Headache was the outstanding symptom; the leukocyte count fell rapidly to 400 per c.mm., the granulocytes disappearing. A transfusion wound failed to heal, a thick whitish-gray ulcerating lesion appearing at its site. The patient died seventeen days after onset of severe symptoms and nine and a half weeks after onset of upper respiratory symptoms. Anaërobic blood cultures showed a growth of streptococci. Transfusion of blood and Roentgen ray treatment over the long bones failed to help.

CASE V.—Edward G.,* a lawyer, aged forty-three years, had always been well. On May 9, 1929, he complained of sore throat; his temperature was 102° F. On May 10 temperature was 103° F., and he complained of severe headache. The throat was red and congested. On May 11 there was difficulty in breathing, and he was admitted to the Beth Israel Hospital. The patient was extremely restless and dyspneic, dyspnea being chiefly expiratory. The throat was red and congested; over the tonsillar area was

* We are enabled to report this case through the courtesy of Drs. H. Morrison and L. Wolfson of Boston.

present a patchy, grayish membrane. The abdomen was distended and tympanitic. Urine showed a strong trace of albumin with numerous red blood cells and granular casts. Hemoglobin was 70 per cent; the red blood cell count, 4,270,000 per c.mm.; white blood cell count, 880 per c.mm. Differential count of 20 white blood cells showed 1 polymorphonuclear cell, 7 lymphocytes and 12 monocytes. Transfusion of 500 cc. of blood was given, the white blood cell count rising to 3000 per c.mm. after transfusion. The next day the count was 1200 per c.mm. Blood culture showed no growth. The icterus index was 26, definitely elevated. The patient was now *in extremis*. A tracheotomy was performed for respiratory relief. On the afternoon of May 12 the temperature rose to 104° F., pulse to 130 per minute, respirations to 40 per minute and the patient died. Autopsy was not obtained.

This was, then, another fulminating case occurring in a previously healthy man, aged forty-three years, whose total illness lasted but three days and was characterized by high fever, sore throat, expiratory dyspnea and an extremely low leukocyte count.

Case VI.—A coppersmith,* aged forty-six years, developed sore throat and fever on August 13, 1929. Two years previously he had been rejected by a life insurance company because of hypertension and diabetes. Eight weeks before his illness began he had noticed a sore on his penis, and in four weeks a rash appeared over his entire body. A doctor found the blood Wassermann test positive, and gave the patient an injection into a buttock; this was followed by severe local reaction associated with pain and fever. He was then given three intravenous injections of arsphenamin. On August 12 a blotchy eruption appeared over most of the body. On August 13 there was sore throat, malaise and temperature of 103.6° F. On August 16 he became delirious, and was admitted to the Beth Israel Hospital the following day. Examination disclosed an obese, markedly dyspneic man in general distress. He was moderately cyanosed and slightly jaundiced. Pulse was 140 and respirations 44 per minute. A fine macular erythematous rash was present over both legs and at the sides of the abdomen. In addition, numerous purpuric spots were present on the legs. A superficial abscess was seen over the right buttock; there was a slight amount of purulent material, but no induration could be made out. Ophthalmoscopic examination revealed a large, fresh circumscribed hemorrhage in the left fundus. Herpetic lesions were present on both lips. On the buccal mucous membrane and on the soft and hard palates there was a diffuse ulceration and desquamation of whitish necrotic mucosa. Both tonsils were swollen and red, their surfaces ulcerated, a necrotic whitish membrane being present; the tonsillar pillars were also involved. The signs of pulmonary consolidation were present at the base of the right lung. Urine showed a slight trace of albumin and numerous fine, brown granular and cellular casts. Hemoglobin was 65 per cent (Tallqvist); red blood cell count, 3,680,000 per c.mm.; white blood cell count, 1100 per c.mm. Differential count of 100 white blood cells showed no granular cells whatever; lymphocytes, 92 per cent; monocytes, 8 per cent. Platelets were abundant on smear.

On the evening of admission auricular fibrillation was noted; cyanosis became extreme. A Roentgen ray of the lungs showed probable bronchopneumonia. Blood nonprotein nitrogen was 88 mg. per 100 cc. Blood

* We are enabled to report this case through the courtesy of Dr. Bernard Appel of Boston.

culture showed a growth of pneumococcus Type IV. Blood Wassermann reaction was positive. On August 18 the patient died. A blood smear taken a half hour before death showed fairly numerous white blood cells (estimated white blood cell count, 4000 to 5000 per c.mm.). The cells were all lymphocytes, most of them large. About 10 per cent were in all probability lymphoblasts; these were large; the nucleus finely reticulated and containing 1 to 3 nucleoli. Autopsy was not obtained.

In brief, this was a case of agranulocytosis in a man, aged forty-six years, who developed sore throat and high fever after four antiluetic treatments for secondary syphilis. In addition to the ulcerating lesions of agranulocytosis present in the throat, there was a macular rash, as well as a purpuric eruption. The latter was considered to be toxic in nature since the platelets were abundant. There was slight icterus and a Type IV pneumococcus bronchopneumonia. Just before death large numbers of early lymphocytes appeared in the peripheral blood.

Case VII.—Seen by one of us (W. D.) with Drs. H. J. Inglis, of Boston, and S. W. Cornish, of Everett, Mass. A woman, aged forty-eight years, took to bed on December 8, 1929, because of extreme fatigue and weakness. For years she had been subject to attacks of bronchitis and asthma, but had been free from attacks in the past year. She had had frequent attacks of tonsillitis. Her two children had been delivered by Cesarean section. In the past year her menstrual flow had been irregular, at times scanty, at times profuse. Since the end of November, 1929, she had felt tired and without ambition, so that finally on December 8 she took to bed. She felt "dry" all over the body, particularly in the mouth, and drank large quantities of water without relief to her thirst; her appetite was poor. She developed running nose and what was considered to be sinusitis. On December 10 she complained of severe burning sore throat and a sore mouth. On the following day a membrane was noted on one tonsil and then on the other. Two throat cultures were negative for diphtheria bacilli; in spite of this she was given diphtheria antitoxin. Weakness increased; temperature fluctuated between 101° and 102° F. There was at times slight delirium. She was seen in the morning of December 24 by Dr. Inglis, who made the diagnosis of agranulocytosis; white blood cell count taken by him was 2400 per c.mm.; differential count of the white blood cells showed polymorphonuclear cells, 20 per cent, and lymphocytes, 80 per cent. Examination on the evening of December 24 revealed a haggard-looking woman lying flat in bed. She was in very poor condition and seemed moribund. There was a marked odor to the breath as though of putrefaction. Tracheal râles were heard. Temperature was 103° F.; pulse, 120; respirations, 30 per minute. Several areas on the buccal mucous membranes were covered with a grayish-white membrane; the smaller ones resembling bits of curdled milk. Several small areas of ulceration and membrane formation were present on the gums and a few on the anterior portion of the tongue. The tonsils were enlarged and reddened; on each of them was seen a thick, grayish-white, firmly adherent membrane. A few slightly enlarged cervical lymph nodes were felt. The liver was palpable two fingers' below the right costal margin; the spleen could not be felt. The skin was inelastic; there was no icterus and no petechial spots were present.

On December 25, the next morning, the patient was removed to the Lawrence Memorial Hospital, Medford, Mass., where she was given a

transfusion of 500 cc. of whole blood by Dr. A. Kimpton, and 10 cc. of whole milk intramuscularly, as well as 500 cc. of salt solution subpectorally and 10 per cent glucose solution by rectum. Temperature fluctuated between 100° and 102° F. On December 26 the patient was much brighter, though her temperature was higher; she was again given 10 cc. of whole milk intramuscularly. There was from then on continued improvement. The temperature fell gradually to normal by January 1, 1930, and the throat and mouth lesions gradually healed. The last lesion to heal was a large ulceration on one side of the nasal septum. She was discharged home well on January 12, 1930. The laboratory data are given in the form of a chart:

CASE VII.—MRS. W. S. T.

	Dec. 24.	Dec. 25.	Dec. 27.	Dec. 29.	Jan. 1.	Jan. 4.
Hemoglobin	70					
Red blood cells (millions)	4.2					
White blood cells	1,500	10,000	8,000	7,600		
Platelets	340,000					
Neutrophils (per cent)	1	.....	22	43.2	38	50
Mature	.....	.....	2	8.8	22	41.5
"Band"	.....	.....	16	32.4	16	8.5
"Young"	.....	.....	4	1.2		
Myelocytes	1	.....	—	0.8		
Lymphocytes (per cent)	99	.....	50	45.2	40.5	35.5
Small	68	.....	21	10.4	40.5	
Large	31	.....	29	28.0		
Plasma	.....	.....	.....	6.8		
Monocytes (per cent)	—	.....	28	11.6	21.5	14.5
Ordinary	.....	.....	19	10.4	21.5	
Histiocytes	.....	.....	9	1.2	—	

This is then a case of agranulocytosis in a woman, aged forty-eight years, who had never been robust. After two weeks of weakness and thirst, she developed a nasal discharge and a sore throat with temperature of 102° F. A membrane appeared over the tonsils, gums and buccal mucosa. The patient became delirious and moribund. Granulocytes disappeared almost entirely from the circulation. A blood transfusion was given; before this, however, the white blood cell count was said to have risen from 1600 to 10,000 per c.mm. Unfortunately blood smears were not taken. The rise in white blood cell count was apparently due (1) to an outpouring of immature bone-marrow cells, and (2) to a very marked increase both in lymphocytes and monocytes. Histiocytes were seen during this stage. Continued clinical improvement, associated with rise in polymorphonuclear count took place, so that the patient was discharged well, about five weeks after onset of her acute illness.

CASE VIII.*—S. W., a baby aged sixteen months, became ill on February 26, 1930, with fever, listlessness and cough. At five months and at eight months she had been ill with discharging ears. At one year she weighed but 16 pounds. On February 27 the temperature was 102° F. On March 2 she was admitted to the Beth Israel Hospital. She was quite "toxic" and prostrated. Both ear drums were reddened. The lips

* This case is reported through the courtesy of Dr. Max Tennis of Boston.

were slightly cyanotic. The pharynx was intensely reddened, as were the tonsils, but no membrane was present either on the fauces or on the buccal mucosa. A few medium and coarse crepitant râles were heard over both upper chests. The diagnosis of acute upper respiratory infection, acute bronchitis and questionable bronchopneumonia was made. White blood cell count was 5,500 per c.mm. and not 1 granulocyte could be found on smear. Roentgen ray of the chest on March 3 showed the markings in both upper lobes exaggerated and the hilus regions considerably increased in width and density. The findings were said to be consistent with an acute bronchitis. On March 6 dullness at the base of the right lung was noted with bronchovesicular breathing and coarse crepitant râles. On March 7 there was a purulent secretion from the right ear. The child was extremely ill from March 2 to March 5, but on March 6 there was slight improvement; on March 7 marked improvement. She was happy and smiling on March 9. The temperature for the first three days in the hospital ranged from 103° to 105° F.; on March 7 it reached normal and, except for slight evening rises, remained at normal from that time on.

The blood picture was an extremely interesting and unusual one. There was at first complete agranulocytosis; the lymphocytes were normal in absolute number, but there was a marked mono- and histiocytosis. The histiocytes were typical, and were checked by supravital staining in a hot box. After this marked monocytosis there was an intense lymphocytosis followed by gradual increase in the granulocytes. At first the polymorphonuclear cells seen were almost entirely metamyelocytes or myelocytes—as recovery advanced, the mature forms gradually increased in number. This is brought out in the appended chart.

Case VIII.—S. W.

	Mar. 2.	Mar. 3.	Mar. 5.	Mar. 6.	Mar. 7.	Mar. 8.	Mar. 9.	Mar. 11.
Red blood cells	5,100,000	....	....	....	....	....	5,300,000	
White blood cells	5,500	5,500	12,000	10,000	18,000	18,300	15,000	15,000
Neutrophils per cent	0	1	8.8	6.5	25.0	36	45.5	56.5
Mature	....	—	1.2	1.0	19.5	....	36.5	51.5
"Band" forms	....	1	5.6	5.5	4.5	....	5.0	5.0
"Young" forms	....	—	1.2	—	0.0	....	4.5	0.0
Myelocytes	....	—	0.8	—	1.0	....	0.5	0.0
Lymphocytes per cent	57.0	65.5	60.4	82.5	53.0	56.0	40.5	31.5
Small	30.5	45.5	39.6	65.5	41.0	....	31.5	
Large	23.0	18.0	16.8	15.5	14.0	....	8.0	
Plasma	3.5	2.0	3.2	0.0	....	....	1.0	
Lymphoblasts	....	1.0	0.8	1.5				
Monocytes per cent	43.0	33.5	30.4	10.0	17.5	7.0	12.0	10.0
Ordinary	24	18.5	29.6	....	17.0	....	11.0	9.0
Histiocytes	19	15.0	0.8	....	0.5	....	1.0	1.0
Eosinophils	0	0	0	1.5	2.5	1.0	1.0	1.5
Basophils	0	0	0.4	....	....	1.0	1.0	0.5

Case IX.—A boy, aged two years and four months, was admitted to the Beth Israel Hospital on March 14, 1930. Family and past history were not significant. Three months previously the right ear drum had been lanced because of otitis media. Convalescence had been uneventful until two weeks before admission, when aural paracentesis again became necessary. At this time the child became feverish and developed enlarged maxillary and cervical glands on the affected side. He had been becoming increasingly pale, weak and inactive during the three months of illness. Examination on admission showed a very restless, very pale boy. There was a thin mucoid discharge from his right ear. The tonsils were enlarged and ragged. The spleen, which was soft, was felt almost to the pelvic brim. The liver edge was just palpable. The submaxillary and supraclavicular lymph nodes were moderately enlarged. The skin showed

numerous petechiæ and a few ecchymotic areas. The temperature was 104.5° F. Urine, stool, blood Wassermann reaction, tuberculin test and blood cultures were all negative. The hematologic findings are given in the following table:

CASE IX.

	March 14.	March 15.	March 16.	March 17.	Transfusion. March 18.	Transfusion. March 19.
Hemoglobin	50	38	25	21	40	
Red blood cells (millions)	1.91	1.77	1.58	1.41	3.55	2.05
Platelets	....	..	39,000			
White blood cells	3,600	6,800	3,200	3,000	2,000	2,500
Neutrophils	....	..	26	12		
Mature	....	..	5	2		
"Band"	....	..	14	7		
"Young"	....	..	5	—		
Myelocytes	....	..	2	3		
Lymphocytes	....	..	74	88		
Monocytes	....	..	0	1		

The child was extremely ill. On March 18 transfusion of 200 cc. of citrated blood was given. This had no effect on the illness and the child rapidly became moribund. On the night before death almost every traumatized area was markedly ecchymotic. These areas became almost black and markedly edematous; some of them oozed serum. On March 20, 1930, the child died.

Postmortem examination showed slight jaundice. Many enlarged edematous mesenteric lymph nodes were seen. The right pleural cavity showed 70 cc. of fluid. The spleen was much enlarged (120 gm.), firm and its markings almost entirely obliterated. Peyer's patches were considerably enlarged. Numerous petechiæ were present throughout the viscera. The tonsils were necrotic and gangrenous. Microscopic examination disclosed hemorrhages into various organs. The stellate cells of the liver were exceedingly prominent and apparently hypertrophied; several of them contained phagocytized material. The spleen showed hypertrophy of the reticuloendothelial cells.

The bone marrow showed: (1) Patchy destruction, with a good deal of cellular debris; a few scattered groups of normoblasts and myelocytes were seen. (2) Extreme swelling of the reticuloendothelial cells which appeared at times to contain phagocytized material, particularly bacteria. (3) An increase in myeloblasts. Megakaryocytes were rarely seen.

This was then an atypical case of agranulocytosis in a young child who suffered from long continued sepsis. Toward the end there was an almost complete aplasia of the bone marrow. The postmortem findings were distinguished by hypertrophy of the reticulo-endothelial cells, particularly in the liver and bone marrow.

Analysis of Symptoms. *Age.* Aside from the patient, who was fifty-nine years of aged and the 2 infants, the others were in the fourth decade of life; from forty-one to forty-eight years of age. Malignant neutropenia in children is rather rare, and has to our knowledge

not previously been reported in infants under two years of age. Schwartz,[6] in 1904, observed a child of nine years who died, presumably of general sepsis, after a leukocyte count of 600 per c.mm. Other cases have been reported by Bantz,[7] Tokue and Yasumoto,[8] Dwyer and Helwig,[9] von Haken,[10] Dufourt,[11] Chistoff,[12] Weiss,[13] and Dodd and Wilkinson.[14] Our 2 cases in infants are apparently the twelfth and thirteenth cases in children under ten years of age.

Sex. In our series of 9 cases, 5 were in females and 4 in males. Most writers agree that the disease is seen more frequently in women, Hueper[15] finding a ratio of 3.5 women to 1 man.

Previous Health. In 8 of these patients, there was the same history of weakness or lack of vitality for a varying period before onset of the present condition. Thus, in Case I, there had been debility for years, and weakness for three months; in Case II, the patient had not felt "up to par" for about a year; in Case III, diabetes had been known to exist for some ten years, and weakness had been present since cholecystectomy four months previously; in Case IV, there had been lack of energy for years; in Case VI, hypertension and diabetes had been present for at least two years; in Case VII, the patient had never been robust and had had asthma for years; in Case VIII, the child was decidedly underweight, and had had frequent colds and aural infections; in Case IX, frequent colds and aural infections had also been present for several months. On the other hand, in Case V, the patient had always been well and had been active physically and mentally until onset of his illness. This tendency for agranulocytosis to occur in debilitated persons has been brought out by several authors.

Onset in these cases was usually with fever, chill and sore throat. The high fever and marked prostration was at times out of all proportion to the very few physical signs. In Case I, there was onset with pain in the region of the anus; in Case IV, influenzal symptoms appeared at first; in Case VII, there was marked weakness and thirst. The course was typically rapid, but was gradual in I and IV. In Case I, there was long continued fever and weakness; in Case IV, there was headache, weakness, delirium and fever. The typical anginal picture was present in 5 of the 8 cases (II, III, V, VI, VII). Case I, showed anal ulceration, and Case IV no ulceration on mucous membrane, except that which developed at the site of the transfusion wound. Membrane, if present, was always seen on the tonsils; in addition, the buccal mucous membrane, soft and hard palates, gums and tongue were frequently involved. Jaundice was present in 4 of the 8 cases. Case III was complicated by diabetes and slight acidosis; Case IV by the symptoms of headache, delirium and questionable meningitic signs; Case VI by diabetes, syphilis, antiluetic treatment and bronchopneumonia. The diagnosis was easy in the typical cases, but the long-continued fever with anal symptoms in Case I was puzzling, as was the absence of localizing signs and continued fever in Case IV. The disease lasted

from three days to three months, but 4 of the cases lived for less than ten days after onset. Autopsy was obtained only in Cases I and IX.

Laboratory Data. *White Blood Cells.* The outstanding laboratory finding in this disease is, of course, the marked leukopenia. In a severe case with angina, this may be so low as to be practically uncountable (See Case II). In the mild case with relatively slow course, the white blood cell count may at onset be quite normal (6000 to 7000 per c.mm.) but may gradually fall to 1000 per c.mm. or thereabouts. Complete studies on the changing differential counts of the white blood cells have been made in but relatively few of the reports recorded in the literature, chiefly, it is presumed because of the rapid course of the disease, and second, because of the extreme leukopenia which makes finding of the cells difficult. The opportunity for careful study of the differential blood picture was offered in Case IV, which was relatively slow in course; in Case VII, in which the recovery phase was fairly well studied; and in Case VIII, in which the recovery phase could be closely followed. In Case IV, the gradual disappearance of granulocytes, most of which were immature forms, could be followed. This observation is interesting in that several authors have pointed out that no immature forms are seen in agranulocytosis.

Immature forms of polymorphonuclear cells were also seen in Cases I (myeloblasts), III, VII, VIII and IX. A terminal rise in immature polymorphonuclear cells has been commented upon by Krumbhaar[16] who, observing this phenomenon in fatal cases of mustard-gas poisoning associated with marked leukopenia, called it a "myelocyte crisis." This is reminiscent of Schilling's "degenerative" type of polymorphonuclear response,[3] in which although immature polymorphonuclears are numerous the total white blood cell count becomes gradually diminished. This was due, Schilling felt, to a degeneration of the marrow by toxins or bacteria themselves. Its mechanism may be explained thus: (1) The toxic or infectious agent destroys most of the granulocyte-forming tissue in the marrow; (2) the remaining granulocytes, however immature they may be, gradually or suddenly appear in the blood stream until finally the available stock or granulocytes becomes totally exhausted. Schilling felt that this idea of a "degenerative shift" was a theoretical conception as yet unsupported by experimental proof; recent experiments on the production of agranulocytosis by Fried and the senior author[32] have gone far toward proving the correctness of this conception. The reverse of this "degenerative" process was seen in the recovery phase as in Cases VII and VIII, in which, after almost complete disappearance of granulocytes, there was suddenly a marked outpouring of immature polymorphonuclear cells, as well as of histiomonocytes.

The lymphocytes and monocytes may at first be present in their normal absolute numbers, the entire drop in leukocyte count being due to disappearance of granulocytes. As the disease progresses

and becomes more and more severe, there appear to be, not only depression of the granulocytic tissue, but marked depression in lymphoid and reticuloendothelial tissue as well, so that the absolute numbers of lymphocytes and monocytes become much reduced. At times, however, as in Case VI, there was a terminal rise in white blood cells which was found to be due to an outpouring of early lymphocytes. The marked reduction in lymphocytes is at times quite striking. Its mechanism is obscure. It is well known that there is a relative and absolute diminution in lymphocytes, often of striking degree at the inception of many acute infections. If the infection becomes very severe, lymphocytes tend to disappear from the differential count; if the infection becomes lessened, lymphocytes increase. The severity of the infection or toxemia causing agranulocytosis may be responsible for the inhibition of the lymphoid tissue, or it is possible that an actual destruction of this tissue as well as of the bone marrow may be present. This would cause not only neutropenia, but lymphocytopenia as well. Regarding the monocytes, in Case VII, associated with a sudden reversal of count, the monocyte percentage rose from zero to 28, several of the monocytes being definitely immature and several being typical histiocytes. In Case VIII, there was a mono- and histiocytosis with a fairly high total leukocyte count when the patient was first seen. In Cases III and V, the monocytes at first outnumbered the lymphocytes, and in each case histiocytes were seen. This monocytosis has been commented upon by several observers and is apparently due to marked proliferation of the reticulo-endothelial system, particularly in the spleen.

Red Blood Cells. The red blood cell count is only slightly affected in this disease. If, however, the illness lasts more than the usual ten days, the red blood cell count may fall to fairly low limits. In Case I, in which the erythrocyte count became very low, aplastic anemia was simulated; this case, to be sure, was atypical. In the ordinary case, however, the color index is less than one and the blood findings are those of a secondary anemia, the red blood cells being more or less achromic and their average diameter less than 7 micra. The achromia, low color index and small average red blood cell size serve to differentiate the case from one of primary aplastic anemia.

The hemoglobin and red blood cell counts in the above cases follow:

	Hemoglobin.	Red blood cell counts.
Case 1	60–17 (S)	3,235,000 to 850,000
Case 2	80 (T)	4,500,000
Case 3	85 (T)	4,100,000 to 3,600,000
Case 4	78 (S)	4,460,000 to 3,800,000
Case 5	70 (T)	4,270,000
Case 6	65 (T)	3,680,000
Case 7	70 (T)	4,330,000
Case 8	65 (T)	5,100,000
Case 9	50–21 (S)	1,910,000 to 1,410,000

The Blood Platelets. There has been some discussion as to the numbers of platelets in this condition. Most authors are agreed as to the normal or increased numbers of blood platelets present. (Stocké[17].) The abundance of platelets serves as an important point of differentiation from aplastic anemia due to benzol or from unknown causes. This point has been brought out by one of us recently.[18] The differentiation from benzol aplastic anemia may at times prove important from a medicolegal aspect. Is the extreme leukopenia due to benzol or to the unknown toxic or infectious agent causing agranulocytosis? As with the red blood cell count, the count of the blood platelets becomes reduced if the disease is of fairly long duration and the bone marrow becomes more or less aplastic, but ordinarily the patient dies before this eventuality occurs. Counts or estimations of the blood platelets in the above cases are as follows: (it is of course recognized that the number appearing on a smear do not afford a very reliable basis for evaluation.)

Case 1		100,000 per c.mm.
Case 2		Abundant on smear.
Case 3		Abundant on smear.
Case 4	April 25	316,000 per c.mm.
	April 29	155,000 per c.mm.
Case 5		Abundant on smear.
Case 6		Abundant on smear.
Case 7		378,000 per c.mm.
Case 8		Abundant on smear.
Case 9		39,000 per c.mm.

Blood Cultures. In the 9 cases reported here, blood cultures were done in 6; in 4 of these, there was no growth. In Case IV, there was a growth of streptococcus which occurred under anaërobic conditions; blood, however, taken from the patient on the following day and injected into rabbits and guinea-pigs failed to produce any clinical or hematologic changes. A mouse injected intraperitoneally with a culture of the anaërobic streptococcus died in nineteen days. Postmortem examination showed general peritonitis. Spleen emulsion from this mouse injected into another failed to produce any disease and the animal was alive and well for at least two months after the injection.

In Case VI, there was a growth of pneumococcus, but this was undoubtedly due to the fact that a pneumococcus pneumonia was present in addition to the agranulocytic process.

Positive blood cultures have been reported by several observers and the organisms found have been ascribed by some to be the cause of the agranulocytosis. Several authors have described the finding of Bacillus pyocyaneus in cultures of the blood.[19,20,21] Injection of this organism into animals has at times caused some disappearance of granulocytes. The opinion that the organisms found were the cause of the disease does not, however, seem well substantiated.

It may well be that these organisms are secondary invaders, growing profusely in a system devoid of leukocytes.

Urine. In 2 of the cases, sugar was found in the urine, but in these 2 cases diabetes had been known to be present for some time. Albumen and granular casts in varying amounts were found in 4 of the 5 cases in which the urine was examined. This finding, due apparently to acute toxic or bacterial involvement of the kidneys has been commented upon by several observers.[21,22]

Bone Marrow Biopsies. These are important in enabling us to study the mechanism of the agranulocytosis while the patient is still alive. Furthermore, the fresh bone-marrow biopsy is immeasurably superior to the autopsy specimen, even if postmortem examination is done within a few hours after death. Biopsy of the sternal bone marrow is the method par excellence for the exact differentiation between agranulocytosis and certain cases of aplastic anemia, and acute lymphatic or monocytic leukemia, since this bone tends to maintain "red" marrow more frequently than the long bones.

Biopsies of the sternal bone marrow were done in 2 cases by the method of Seyfarth.[23] In Case I, the bone-marrow examination failed to disclose anything abnormal; in Case IV, the findings were striking, and similar to those which have been described by Stillman,[24] Zadek,[25] and Schultz and Jacobowitz.[26] In this case, biopsy was performed when the white blood cell count was 600 per c.mm. Bone-marrow smears showed many erythroblastic cells (normoblasts, erythroblasts and an occasional megaloblast), occasional megakaryocytes, but complete absence of both myelocytes and polymorphonuclear cells. Typical myeloblasts (fairly large cells 10 to 12 micra in diameter, with ultramarine blue cytoplasm showing as a rim about a very large oval-shaped nucleus, which contained from 1 to 4 nucleoli) were seen as the only representatives of white-blood-cell-forming elements. Sections showed the majority of the cells to be myeloblasts, the normoblasts being present in good numbers. Several of the myeloblasts were seen in mitosis. These findings served to explain the almost complete absence of granulocytes from the blood stream.

Diagnosis. The diagnosis of agranulocytosis in the typical case is now fairly easy, since the symptom complex has become fairly well known. The sudden appearance of a sore throat in a middle-aged, usually debilitated person, accompanied by chill and high fever, ulceration and then membrane formation in the throat and on the buccal mucous membrane should lead one to suspect agranulocytosis. This is especially true when the fever and toxemic symptoms seem out of all proportion to the small amount of ulceration or membrane formation in the throat. Acute follicular tonsillitis, streptococcic sore throat, Vincent's angina and diphtheria are to be differentiated by appropriate clinical means. The routine

performance of a white blood cell count in at least the suspected cases would of course establish the diagnosis more frequently than is done today. None of the above-mentioned disorders cause leukopenia except possibly in the rare case of streptococcic sore throat with streptococcus hemolyticus septicemia. In the latter condition, the white blood cell count may very rarely be reduced to 4000 or 5000, but the differential count of the white blood cells shows usually at least 85 per cent of polymorphonuclear cells.

The diagnosis in the case without angina, but associated only with fever of more or less long duration and with but few clinical signs is more difficult. Here again, if the rule is made of following along each case of continued fever with frequent counts of the white blood cells and their relative proportions, the diagnosis becomes relatively simple. There are to be sure other conditions in which the white blood cell count is lowered and continued fever is present. Typhoid fever and influenza cause neutropenia, but the white blood cell count rarely becomes less than 4000 per c.mm.; there are, furthermore, at least 25 per cent of polymorphonuclear cells almost constantly present; blood and stool cultures and Widal test establish the diagnosis in the suspected cases of typhoid fever. Generalized rapidly advancing tuberculosis may at times be associated with a marked leukopenia. In a case observed by one of us recently, white blood cell count fell to 3000 per c.mm.; however, the polymorphonuclear cells—mostly immature forms—ranged from 90 to 99 per cent of the total number. Pneumonia, severe streptococcic infections with septicemia may at times cause leukopenia, rarely below 6000 and always associated with a marked preponderance of polymorphonuclear cells. Lymphoblastoma (whether of the lymphosarcoma of Hodgkin's type) has been seen by us recently in 2 cases to cause leukopenia with reduction in polymorphonuclear cells; in these cases, however, the rest of the clinical course served to make the diagnosis of lymphoblastoma the probable one, to be confirmed later by either operative or biopsy findings.

Objection may be made that when the diagnosis of agranulocytosis is made in a doubtful case, it is simply on the basis of a low leukocyte count and absence of granulocytes and not on the presence of a clear-cut disease entity. The same objection may be made, however, for cases of acute leukemia in which the diagnosis is made on the presence of a high white blood cell count and very unusual differential count. As a matter of fact, it is sometimes difficult to differentiate clinically between the two conditions, providing that the leukemia is of the "aleukemic" variety. Low white blood cell counts, common enough in the chronic cases, are rather rare in the acute varieties, whether myelogenous, lymphatic or monocytic. Neutrophilic leukopenia in the leukemias is thought to be due to overcrowding of the bone marrow with the leukemic cells. There is, therefore, rapidly advancing anemia and bleeding due to destruc-

tion of blood-platelet-forming tissue. Bleeding in agranulocytosis is rare, since the blood platelets are (except in the very long-standing case) not reduced; anemia, too, is usually slight. However, as Blumer[27] has brought out, the differential diagnosis between acute leukopenic lymphatic leukemia and agranulocytosis may be so difficult as to be well-nigh impossible. Bone-marrow biopsy will settle the diagnosis in the doubtful case; in lymphatic leukemia there is a tremendous crowding of the marrow with lymphoid cells whereas in agranulocytosis, the white cells are conspicuously reduced, only some myeloblasts being present. This was brought out in a case recently seen at the Beth Israel Hospital in which the clinical as well as the blood picture was consistent either with agranulocytosis, or acute leukemia. Sternal bone-marrow biopsy disclosed large numbers of myeloblasts and histiocytes.

Aplastic anemia may at times be difficult to differentiate from agranulocytosis. However, in the former disease, there is aplasia of the bone marrow as a whole, resulting in a yellow marrow which is completely barren of red cells, white cells and megakaryocytes. This brings about a blood picture characterized (1) by rapidly advancing anemia usually of the hyperchromic type; (2) by leukopenia with disappearance of granulocytes, and (3) by marked reduction in blood platelets resulting in hemorrhages of more or less marked severity. In agranulocytosis, on the other hand, the marrow is unaffected except in its white-cell-forming elements. This results in a marked leukopenia with disappearance of granulocytes, but with only a very slight anemia (which is of the achromic type), and without reduction in blood platelets. As noted above, the platelets are usually abundant in the disease, and there is no tendency to a hemorrhagic diathesis. To be sure, if the disease lasts longer than the ordinary week to ten days, rather marked anemia and moderate reduction in the number of blood platelets ensue. The anemia, however, always remains "secondary:" the cells show achromia and microcytosis.

The differential diagnosis between aplastic anemia and agranulocytosis may at times be important from a medicolegal or industrial standpoint. Has a worker in a factory which uses benzol, agranulocytosis, or has he benzol poisoning? Bone marrow biopsy may at times be resorted to; in aplastic anemia the sternal marrow is yellow, and completely or incompletely devoid of the three marrow elements: red cells, white cells and megakaryocytes; in agranulocytosis, the sternal marrow is red and normal in red cell and platelet-forming elements, but deficient in granulocytes. To summarize, aplastic anemia gives a hyperchromic (high color index) anemia with marked reduction in platelets as well as in white cells; agranulocytosis gives a hypochromic ("secondary") anemia with (usually) abundant platelets.

The diagnosis, then, of agranulocytosis with angina is a more or

less simple one. The cases of agranulocytosis without angina may simulate any febrile disorder associated with a leukopenia and may at times be difficult to separate from such blood dyscrasias as aplastic anemia, aleukemic leukemia and lymphoblastoma.

Prognosis and Treatment. At least 90 per cent of the reported cases of malignant neutropenia have proved fatal. Cases with recovery have been reported by several authors. In most cases, recovery has been ascribed to the modes of treatment instituted. Thus, Friedemann[28] reports 4 cases which recovered after Roentgen ray treatment had been given over the long bones; Wyatt[29] 1 case which recovered after surgical drainage of multiple abscesses; Paroulak[30] 1 case with recovery after repeated transfusions; Call, Gray and Hodges[31] 1 case benefited by Roentgen radiation. Other suggested methods of treatment have been arsenical compounds, antistreptococcic serum, foreign protein such as whole milk, and alcoholic gargles.

In our group of 9 cases, 2 recovered—Cases VII and VIII. In Case VIII there was no question as to the spontaneous recovery; in Case VII, it would seem that the transfusion and repeated injections of whole milk into the buttocks were beneficial. However, in the latter case, the rise in leukocyte count to 10,000 per c.mm. before transfusion would be more consistent with a spontaneous recovery than with one caused by the method of treatment used.

It is our belief at the present time, that recoveries, if they occur, are spontaneous. Recoveries are to be expected, not in those fulminating cases with the typical anginal picture and drop in leukocyte count to a few hundred per cubic millimeters, but rather in those cases, which are more prolonged and milder. It is in these cases, apparently, that the reticulo-endothelial and lymphoid tissues are able to respond and tide the system over until the bone marrow can recover. Rational methods of therapy are repeated transfusions which add necessary polymorphonuclear cells until spontaneous recovery can take place, if it will; and foreign protein therapy which may act by stimulating the reticulo-endothelial tissue. There may be some rationale in roentgen radiation over the long bones in an attempt to stimulate a yellow, inactive marrow to become red and active.

Theories as to Pathogenesis. Numerous theories have been advanced to explain the disease (or symptom complex) of agranulocytosis. What is indeed most puzzling is the almost complete lack of reported cases before Schultz's[1] observations. Most authors are agreed that the blood picture is due to a marked effect on the myeloid cells by a septic or toxic process. What this process may be is as yet unknown. No specific organism has as yet been isolated, though several authors, finding the bacillus of pyocyaneus present, feel that this organism is the cause of the disease. Whatever the organism or organisms may be, it behaves differently from those

bacteria causing ordinary septic processes. It seems useless to conjecture as to whether the patient with agranulocytosis has had a vulnerable or weakened hematopoietic system before onset of the disease. In a complete study of the literature, Stocké[17] concludes that there are imperceptible transitions from pure or typical agranulocytosis to the usual course of sepsis with rather an unusual type of leukopenia, and that agranulocytosis is not a special disease, but an abnormal reaction to sepsis. This is well brought out in the cases described above, all gradations from the typical case to the one of sepsis with atypical leukopenia being seen. One of the authors, with Fried,[32] is at present engaged in a study of experimental agranulocytosis which may throw some light on the pathogenesis of the disease.

Summary and Conclusions. 1. Nine cases diagnosed as agranulocytosis (malignant neutropenia) are reported. Four of the cases were typical of the "angina agranulocytica" described by Schultz, the other five being atypical in one or another feature. Two of the cases were in infants. Two of the cases recovered. In one case arsphenamin injections constituted in all probability an etiologic factor.

2. The diagnosis of the disease, its blood picture, and various clinical features are discussed. The recovery phase, with its marked monocytosis and histiocytosis, was studied in Cases VII and VIII.

3. It is felt that agranulocytosis is a symptom complex, dependent primarily upon an abnormal reaction of the bone marrow to severe sepsis. Gradations can be seen between the typical case with angina, and those cases of sepsis with an atypical leukopenia.

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IDIOPATHIC APLASTIC ANEMIA OR ALEUKIA HEMORRHAGICA.

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The diagnosis and management of aplastic anemia is a problem which has not been entirely solved by modern clinical methods. In fact, little has been added to the certainty of diagnosis or to the success of treatment since Ehrlich described the disease forty-two years ago. Perhaps the greatest forward step has been the discovery of certain etiologic agents as radium, Roentgen rays, benzol and arsphenamin, in which group a large proportion of all reported cases belong. The term idiopathic aplastic anemia or aleukia hemorrhagica has been given to a moiety of cases constituting the remainder.

Textbook accounts of the clinical and laboratory features of this idiopathic type of the disease are brief, often obscure, and sometimes inaccurate, as the number of authentic reported cases is extremely small. The occurrence of 2 cases in the medical wards of the Montreal General Hospital during the spring of 1930 furnished a stimulus for reviewing the recent literature of the disease in order to obtain a composite clinical picture which would be accurate and fairly complete. Sixty-two references were obtained, from which 16 cases [1-14] were selected because they were well investigated clinically and were confirmed by necropsy. The error of accepting incomplete clinical reports for statistical purposes is illustrated by the cases of Bickel[15] and of Opitz,[16] which at postmortem proved to be aleukemic lymphosis. For this reason only the first of the following 2 cases is included with those culled from the literature in this clinical summary. The second case is believed to be an unusual type of aplastic anemia.

Case Reports. CASE I.—V. L., a Czecho-Slovakian, aged thirty-two years, a butcher, was admitted to the Montreal General Hospital on April 4, 1930, complaining of pallor and pain in the heart and back.

The personal history was without incident except for an illness of fourteen days' duration characterized by pain in the "kidneys" in the year 1916, and a gastrointestinal upset in May, 1928. He denied venereal disease and did not use alcohol. His average weight was 136 pounds.

The family history was negative. The father died at seventy-four years. The mother died at fifty-four years of unknown cause. Two brothers and one sister are alive and well.

The present illness began in February, 1930, with mild epistaxis and bleeding from the gums on slight trauma. About March 4 he began to feel tired and weak, and his friends remarked upon his pallor. After March 20 he had spasms of dull, aching pain along the left costal margin and in the small of the back, brought on by exertion and relieved by rest. He admitted to dyspnea only on exertion. He denied gastrointestinal symptoms such as vomiting, diarrhea, soreness of the tongue, and had never had paresthesia of the extremities. He believed that the stool had been black at times shortly before admission, but he had never observed gross blood.

Examination on April 4, 1930, the day of his admission to the hospital, revealed a subicteroid pallor of skin and mucous membranes. The pupils were active. The tongue was not atrophic. The lymph nodes were not remarkable. The lungs were clear. The pulse was 68, the blood pressure 120 systolic and 72 diastolic, and the relative cardiac dullness slightly increased. The liver and spleen were of normal size. The reflexes were active and two point discrimination was excellent (4.5 cm.).

Laboratory Features. 1. The urine was normal. Urobilinogen was present in less than one in ten dilution.

2. The stool showed neither ova nor occult blood.

3. The blood urea nitrogen was 17, the creatinin 1.42, and the blood sugar 65 mg. per cent.

4. Fractional test meal showed the greatest acidity to be forty-five minutes after an Ewald meal, when the free HCl was 35 and the total acidity 52.

5. Combined fluoroscopic and serial plate examination of the intestinal tract was negative.

6. The blood Wassermann test was negative.

7. The initial blood findings were as follows. Red blood cells, 1,130,000; white blood cells, 3150; hemoglobin, 28% (Hellige); color index, 1.2; reticulo-

cytes, 0.5%; platelets, 30,000; bleeding time one-half minute (Duke's method); coagulation time, eleven minutes; retraction of clot slight; Rumpel-Leede test negative; diameter of average red blood cell, 8.6 microns; differential count, polymorphonuclears, 48% and lymphocytes, 52%. Smears were stained supravitally and by Wright's method. The red cells showed comparatively little variation in size and shape without basochromia. No nucleated reds were ever found. The predominating erythrocyte was a macrocyte. The course of the disease and the effect of treatment on the blood values are illustrated by the following table.

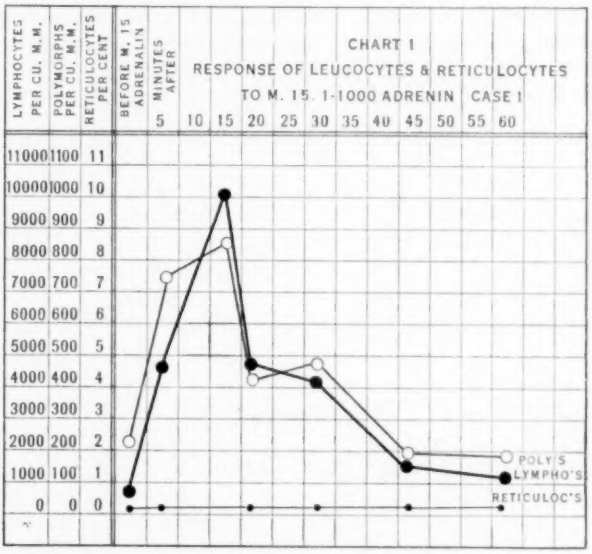
TABLE I.—HEMATOLOGIC DATA OF CASE I.

Date.	Red blood cells in millions per c.mm.	White blood cells in thousands per c.mm.	Hemoglobin.	R. R.	Platelets in thousands per c.mm.	Pn.	Ly.		Red cell diameter.	Treatment.
IV: 14	1.10	5.1	26	0	343	64	36	....	8.1	Stomach extract, Blaud's, grain x three times a day.
17	0.79	2.7	21	0	158	68	28	Eos 4		
19	0.88	....	..	0	....	..	..	....	...	Transfusion.
21	1.09	2.2	25	0	114	59	36	Eos 5	7.9	
24	1.07	2.2	28	0	153	60	40	....	7.6	
26	1.11	3.0	27	0	194	66	33	Bas 1	...	Raw liver pulp half pound daily.
29	....	....	..	0						
V: 1	0.83	2.8	26	0	...	62	35	Eos 3	8.2	
3	....	....	..	0	....	..	..	....	...	Transfusion.
5	1.14	4.4	28	0	240	71	20	My. 5 Metamy 3	8.0	
7	....	....	..	0	....	..	..	....	...	Blaud's and copper added.
12	1.03	6.3	23	0	...	57	43	....	8.0	
14	....	....	..	0						
16	1.09	4.5	22	0	324	62	36	Eos 2	7.9	

From April 4 to May 15 the course was an afebrile one: from May 16 to May 30 a remitting temperature of 101° to 105° F. The final period of pyrexia was associated with an extensive stomatitis. With the exception of the features already mentioned, no changes were observed in the general appearance of the patient other than a slight enlargement of the liver and the development of an apical systolic bruit. The spleen never became palpable and the lymph nodes did not enlarge. The weight was well maintained. From April 29 to May 29 the patient consumed 15 pounds of raw liver pulp. The capsules of iron and copper, which contained Blaud's mass 30 grains and copper (as carbonate) $\frac{1}{8}$ of a grain, were given thrice daily.

Autopsy. At postmortem, petechiæ were observed over the head, neck and left thigh. A few scattered petechiæ were noted beneath the epicardium, and the visceral peritoneum covering intestines and liver. The mesenteric lymph nodes were enlarged and hard. The lungs were negative except for small alveolar hemorrhages and a healed right basal pleurisy. Hemorrhagic areas were found within the myocardium as well as beneath the epicardium. The spleen weighed only 170 gm. It was firm and with distinct markings. Microscopically the architecture was intact. Collections of hemosiderin-bearing cells were present in the pulp. The liver weighed 1770 gm. and appeared grossly normal except for the surface petechiæ. Histologically the only feature was perivascular collections of lymphocytes, but these did not invade the parenchymal cells. The lymph nodes presented no microscopic abnormality. The bone marrow was white and fatty. Microscopically it was composed entirely of fat cells and bloodvessels. Practically

all the capillaries were collapsed. No areas of myeloid or erythropoietic activity were found. Here and there were small hemorrhages. The kidneys showed no remarkable lesions, and the postmortem was otherwise of no clinical interest.



Case II.—P. P., a Russian laborer, aged fifty years, was admitted to the Montreal General Hospital on April 12, 1930, complaining of buzzing of the ears and pounding of the heart.

Personal History. He had always enjoyed good health until the present illness with the exception of otitis media in 1920. He denied venereal disease and the use of alcohol. He was married and had three healthy children.

Family History. He could give no information as to the family history.

History Present Illness. In February, 1930, he began to feel weak and short of breath on exertion. At the same time he noticed the pallor of his skin. About the beginning of March he suffered from headache and pain in the extremities on walking. One week before admission he experienced pain in the pit of the stomach, unrelated to the taking of food, and relieved by some pills purchased from a druggist. He denied soreness of the tongue or paresthesiæ.

Examination on the day of admission, April 12, 1930, revealed a large well-nourished man with extreme subicteroid pallor of skin and mucous membranes. The tongue showed no atrophy. The pupils were active. The ocular fundi showed many small hemorrhages. The lymph nodes were not enlarged or tender. The chest was negative. The relative cardiac dullness was slightly increased. The heart sounds were free from murmurs and the blood pressure was 88 systolic and 50 diastolic. Neither the liver nor the spleen was palpable. Pallesthesia was normally present but two-point discrimination failed at 8 cm.

Laboratory Features. 1. The urine was quite normal. Urobilinogen was present in traces only.

2. The stool showed no ova, blood, or pus.

3. The blood urea nitrogen was 22, the creatinin 1.42, and the blood sugar 143 mg. per cent.

4. The greatest gastric acidity after an Ewald test meal occurred in sixty minutes when free hydrochloric acid was 32 and the total acidity 56.

5. Combined fluoroscopic and serial plate examination of the gastro-intestinal tract was negative.

6. The blood Wassermann test was negative.

7. The initial blood findings were as follows: red blood cells were 1,100,000; white blood cells, 5100; hemoglobin, 26% (Hellige); color index, 1.1; reticulocytes, none; platelets, 343,000; bleeding time, four minutes; coagulation time, five minutes; van den Bergh, negative; Rumpel-Leede test negative; diameter of average red cell 8.1 microns; differential, polymorphonuclears, 64%; lymphocytes, 36%. In smears stained by Wright's method the red cells showed no stippling and only slight basochromia. There was some variation in the size of the cells but no nucleated forms were ever found. The predominating erythrocyte was a macrocyte.

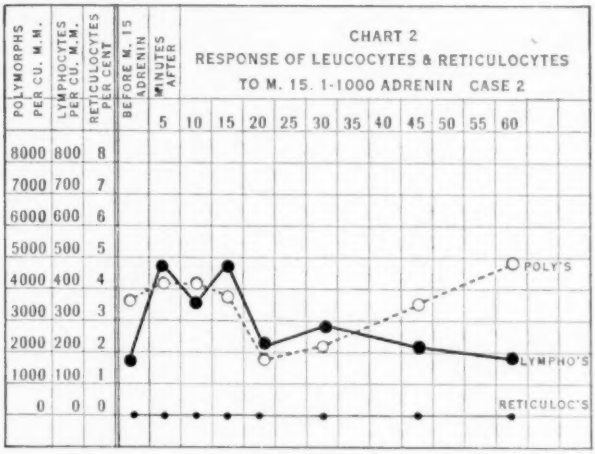
TABLE II.—DATA OF CASE II.

Date.	Red blood cells in millions per c.mm.	White blood cells in thousands per c.mm.	Hemoglobin, %	R. R.	Platelets in thousands per c.mm.	Red cell diameter.	Pn.	Ly.		Bleeding.	Treatment.
IV: 4	1.13	3.1	28	0.5	30	8.6	48	52	....	Purpura	Stomach extract.
10	1.10	...	24	2.8							
13	1.00	2.2	20	0.8							
16	1.34	2.3	25	1.0	8	8.4	41	59	....	Purpura gums	
19	....	...	..	0.8	..	...	..	..	....	....	Transfusion, Fowler's solution.
21	1.37	1.5	33	1.8	9	8.0					
26	1.40	1.1	28	1.0	11	8.2	58	42			
29	....	...	..	1.4	..	...	..	..	....	....	Stomach extract discharge raw liver pulp.
V: 1	0.79	2.3	21	0.8	..	8.2	31	68	Eos 1		
3	....	...	..	0.6	..	...	..	..	....	....	Transfusion.
5	0.96	0.7	30	1.0	48	7.9	22	75	My. 1	None	
12	1.33	1.8	30	0.5	45	7.9	20	80	....	....	Blaud's and copper added.
16	1.10	2.3	22	1.2	..	7.9	14	86	....	None	
20	1.17	2.3	22	1.6	..	8.0	10	90	....	Gums	
26	0.93	2.3	15	1.2	46	7.9	18	82	....	Gums	Transfusion.
29	1.19	1.5	21	0.5	41	8.0	10	78	My. 2		
VI: 2	1.07	1.2	19	0.5	..	7.9	12	84	My. 4	Gums	
7	1.83	1.0	23	0.0	71	7.9	..	..	....	Nose	Transfusion.

The patient was kept *in statu quo* by means of transfusions during the period of hospitalization from April 12 to May 19 when he refused further treatment and went to his home. The course of the disease was an afebrile one from beginning to end. At no time were petechiæ or other hemorrhagic phenomena noted. Neither the spleen nor the liver enlarged. Stomatitis did not occur. The body weight remained at 150 pounds. Frequent Roentgen ray and physical examinations failed to reveal any change in his condition from that noted on admission. He died at his home from extreme anemia in the beginning of July. Autopsy was not obtained.

Historic. The idiopathic type of aplastic anemia was first recognized as a clinical entity by Ehrlich in 1888. He described the hemorrhagic tendency, the liability to necrotic angina, and the aplastic state of the bone marrow. In order to differentiate the idiopathic type from aplastic anemia secondary to such diseases as osteosclerosis, septicemia, and benzol poisoning, Sonnenfeld[17] suggested the term "aleukia hemorrhagica" which has now come

into general usage. Hirshfeld has attempted to classify cases of aplastic anemia upon an etiologic basis. He recognized those due to (*a*) constitutional bone marrow deficiency, (*b*) toxic destruction of marrow as from arsphenamin and benzol, (*c*) a phase or type of pernicious anemia.



Frequency and Conditions of Occurrence. Some idea of the rarity of idiopathic aplastic anemia may be gathered from the paucity of cases recorded in the literature. Probably fewer than 20 cases with postmortem findings were reported during a five-year period when the attention of the medical world was focused upon anemia and its treatment. At the Montreal General Hospital where there are some 2500 yearly admissions, no case of this disease was observed during a ten-year period from 1919 to 1930.

Age. The disease is most common during the period from ten to fifty. Cabot states that 75% of the collected cases occurred before the thirty-fifth year. In the present series 65% were before the age of thirty-five. From one to ten there were 2 cases: from eleven to twenty, 4 cases; from twenty-one to thirty, 3 cases; from thirty-one to forty, 3 cases; from forty-one to fifty, 3 cases; from fifty-one to sixty, 2 cases. The incidence during each decade from eleven to fifty-nine was therefore almost identical. Before and after this age period the disease was found to be somewhat less common.

Sex. In this series the proportion of males to females was 11 to 6, about the same proportion as holds for pernicious anemia. This runs counter to Cabot's observation that the proportion of cases in the female is greater than in pernicious anemia.[23]

Etiologic Factors. The clinical differences between pernicious anemia and the various forms of secondary anemia are such that the two diseases may be readily differentiated, but this does not hold for idiopathic aplastic anemia and that due to recognized causes such as Roentgen rays, radium and benzol. Clinical, hematologic

and postmortem findings are almost identical in the two types of the disease as illustrated by the reports of Sweeney[18] and of Ugriumow and Idelsohn.[19] The presumption then is that the idiopathic type of the disease is due to some noxa with properties similar to those known to cause marrow aplasia. It may be that some cases are due to a constitutional bone-marrow deficiency as Hirshfeld has suggested, but there is scanty if any proof of such a hypothesis. Instances of the disease have occurred in conjunction with malaria (Haridas[20]), syphilis (Chevallier and Flandrin[21]), and chloroma (Herz[22]), but a connection between these diseases was not definitely established in the reported cases.

Pathology. The essential features of aplastic anemia are the result of atrophy of the bone marrow. The hemorrhagic phenomena, though not essential, are almost always present as the megakaryocytes which produce platelets are particularly susceptible to the unknown noxa. Examination of the bone marrow obtained at postmortem in 16 cases and by biopsy in the remaining one showed the following results. The marrow was yellowish-gray and fatty in 15 cases, while in 2 it was reddish in color. As a general rule when it was obtained from the ribs and vertebral bodies it was redder than when taken from the long bones. Myeloid activity indicated by foci of maturing cells in the fatty marrow tissue was moderate in 3 cases, slight in 4, and not present at all in the remaining 10. Evidence of erythropoietic activity was found in only 4 of the 17 cases. Megakaryocytes were observed occasionally in the marrow in 3 cases, in moderate numbers in 1 case, and not at all in the remainder.

The liver was not enlarged at postmortem in any of the cases. The spleen was of normal size or atrophied in 12 cases. In 1 case it was considerably enlarged because of infarcts, while in the remainder the enlargement was slight. Myeloid metaplasia was found in the liver, the spleen, and the lymph nodes in Baisch's case which was a child of four and a half years. The bone marrow in this case was also quite active in appearance and yet there were only 840,000 erythrocytes and 125 polymorphonuclear leukocytes per cubic millimeter of blood. As a rule the hemorrhages were petechial in type, and were widespread, involving skin, mucous membranes and parenchymatous organs. They were particularly observed beneath the serosal covering of the liver, the bowel, the heart, and the lungs. Gross bleeding frequently occurred from ulcerations in mouth and intestinal tract. Atrophy of the tongue and stomach and degeneration of the posterior or lateral spinal tracts was not present in any of the cases. Microscopically nearly all cases showed some degree of hemosiderosis of liver and spleen due to absorption and alteration of extravasated blood by the reticuloendothelial cells of these organs.

Death resulted directly from the extreme anemia in 11 cases.

Two patients literally bled to death. In 1 case exitus was due to septicemia originating in the necrotic angina, and in 2 others to a terminal pneumonia. One case died from a progressive paraplegia caused by numerous hemorrhages into the substance of the brain.

Signs and Symptoms of Aplastic Anemia. In about one-half of the cases the first symptoms were referable to the anemia, as weakness, lassitude, shortness of breadth and palpitation of the heart. The onset was frequently so insidious as not to be recognized by the patient until the pallor was extreme. In 7 cases hemorrhage was the presenting symptom. The most common initial sites of the hemorrhage were the nose, the gums, and somewhat less frequently the gastrointestinal tract and the kidneys. One case was first seen because of joint pains and another because of ulcerative stomatitis. As a rule, however, careful questioning elicited a train of symptoms suggesting an antecedent anemia.

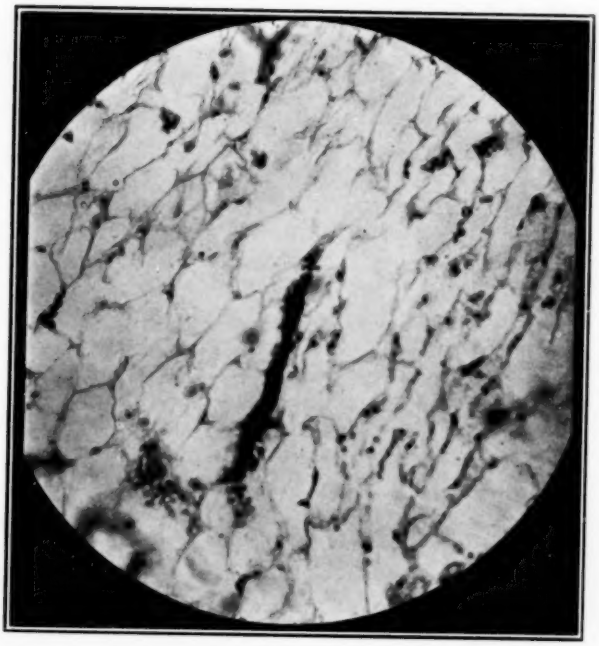
The condition of the patient was to a great extent dependent upon the stage at which the case came under observation. Early in the course of the disease anemia was usually the only obvious feature, and was more often of the waxy than of the subicteroid type. An apical systolic murmur was a frequent finding but the heart was not often enlarged. Examination otherwise revealed only a few petechiæ in most instances.

Later in the course of the disease hemorrhage is the striking feature. Many of the cases were not seen until copious bleeding from the nose, mouth, or gastrointestinal tract forced them to seek medical treatment. On the other hand, no hemorrhagic phenomena may be present at any time as in 4 cases of the series. In 7 cases petechiæ in skin and mucous membranes were noted at the first examination, and in 6 these developed later. Ten cases died without developing an ulcerative stomatitis. One case showed necrotic ulcers in the large bowel. The course of was sometimes fulminating and rapidly fatal as in Ellmer's case, a man, aged forty-four, who literally bled to death in eight days following the appearance of petechiæ on his face. On the other hand, Holboll's case lived for five years after the anemia made its appearance. Ten of the cases died within three months of the time that the first symptoms were noted.

The degree of pyrexia depends largely upon the degree of secondary infection though most cases had a mild fever from the beginning. The terminal stage of the disease was usually ushered in by hyperpyrexia as in Case I.

The Laboratory Features. The urine frequently showed blood if the hemorrhagic tendency was marked. Urobilinogen was present in increased amounts in only 3 cases.

Gastric analysis was carried out on only 5 cases of the series. All of these showed free hydrochloric acid in normal or slightly decreased amounts. This fact alone would seem to place the disease in a different category from pernicious anemia, so that the transi-



Photomicrograph of bone marrow from femur of Case I. The dark line in the center is a small bloodvessel cut rather longitudinally. To its right is a small clump of maturing erythrocytes. The remainder consists chiefly of fat cells and capillaries.

tions between the 2 diseases, as suggested by Cabot,[23] would seem to be extremely unlikely.

The blood picture is practically diagnostic of the disease. All the cellular elements suffer in most cases. Rarely the unknown noxa appeared to select one type of cell as in Case II. The average figures for the various blood determinations are seen in Table III.

TABLE III.—BLOOD FIGURES IN IDIOPATHIC APLASTIC ANEMIA.

	Average initial.	Average terminal.	Lowest count.
Erythrocytes . . .	1,500,000	1,000,000	500,000
Leukocytes . . .	2,200	1,000	250
Hemoglobin . . .	34	29	19
Platelets	49,000	21,000	None present
Color index . . .	1.2	1.5	

The color index in this series was found to be at unity or above it. This runs counter to the prevailing belief. In 11 of the 17 cases the index was above unity and in 3 it was just one. Prolongation of the bleeding time, a positive Rumpel-Lœede test, and poor if any retraction of the clot invariably followed marked reduction of the platelets and the appearance of the hemorrhagic phenomena. Evidence of regeneration of blood elements was usually limited to the occasional appearance of a normoblast and small percentage of reticulocytes. Nucleated red cells were found at rare intervals in only 3 cases. The reticulocytes rarely ever rise above 1% though in one case they reached 3 per cent on one occasion. In Case II no reticulocytes were ever found though they were searched for every alternate day. Stained blood smears showed little variation in the size, shape, or stained properties of the erythrocytes, and punctate basochromia was not observed. The type of erythrocyte in this series was a macrocyte. The average red cell diameter in 3 cases were 8.3, 9.0, and 8.6 microns. In the other case where measurements were given the cell volume was 110 cubic microns, a figure well above the normal. It is of interest that the average cell diameter, which was considerably above normal in Case I at the beginning of the period of observation, was of normal size toward the termination of the illness.

The differential count of leukocytes practically always showed that the reduction in the total number of cells was at the expense of the polymorphonuclears. The average proportion of polymorphonuclears to lymphocytes in the series was 22 to 70. In 4 cases myelocytes were found from time to time in percentages varying from 1 to 5. Eosinophils were rarely found. The serum gave the van den Bergh reaction in only 1 case.

Differential Diagnosis. The diseases from which aplastic anemia must be distinguished are essential thrombocytopenic purpura, secondary aplastic anemia, agranulocytosis, and aleukemic lymphosis. As a rule the disease may be distinguished from Werlhof's purpura without difficulty. In the latter disease the polymorphonuclears are normal or increased, and the anemia is severe only after

prolonged bleeding. Hemorrhage results in a marked increase in the reticulocytes along with other signs of active regeneration, which are entirely lacking in aplastic anemia.

The secondary type of aplastic anemia must be ruled out largely on the basis of history of exposure to one of the agents capable of producing the disease, or the discovery of a cause on careful routine examination, for the 2 diseases are practically indistinguishable on the basis of most clinical and laboratory features. In agranulocytosis there is little or no anemia, and no reduction in the platelets, the former an essential of aplastic anemia. The differential diagnosis of aplastic anemia from aleukemic lymphosis is fraught with the greatest difficulties and is sometimes impossible during life. When the leukemia manifests itself by enlargement of the liver, spleen and lymph nodes, no great difficulty presents itself, but there are unfortunately instances where the leukemic process does not lead to these changes, as in the cases of Bickel and Opitz. The 2 diseases may then be indistinguishable until the microscope has revealed lymphatic infiltration of parenchymatous organs.

The 2 cases reported here presented the usual diagnostic difficulties. In the first the possibility of aleukemic lymphosis was entertained even at postmortem until a microscopic study was made.

The findings in the second case, which unfortunately was not confirmed by autopsy, was far from being typical of the disease. So far as the erythropoietic process was concerned, observations suggested absolute aplasia. At no time was there the slightest evidence of erythrocyte formation such as reticulocytes or other immature forms. On the other hand, the leukocyte and thrombocyte levels were fairly well maintained so that neither infection nor hemorrhagic symptoms made their appearance. It seemed as though the unknown noxa had exerted a selective action, picking out the erythrogenic portion of the marrow.

The Adrenalin Test for Bone Marrow Function. Berchtold[24] made the experimental observation that adrenalin causes a marked increase in the number of red and white cells in the blood of the nutrient vein of the tibia. Use has been made of this observation in the diagnosis of cases of aplastic anemia.[25] The leukocyte and differential counts are made every five minutes after a hypodermic injection of fifteen minims of 1 to 1000 adrenalin hydrochlorid solution. An almost immediate increase in the leukocyte count results, presumably due to splenic contraction. If the bone marrow is completely aplastic, the increase in leukocytes will be largely of the mononuclear variety. If this is not the case, the adrenalin will cause an outpouring of young marrow cells, which will be evident in the differential count. We have supplemented the test by counting the reticulocytes at the same time. The charts of Cases I and II show the absolute numbers of polymorphonuclear cells, the mononuclears, and the reticulocytes at intervals during the first hour after the adrenalin. Whatever may be the explanation

of the changes which have occurred, it is certain that no immature cells made their appearance, thus favoring the diagnosis of aplastic anemia.

Prognosis. The prognosis in aleukia hemorrhagica is almost always hopeless. The average duration of the illness in the 17 cases reviewed was eight months, the shortest eight days, and the longest five years. Ten of the cases were dead in three months from the onset of the first symptoms. Upham and Nelson[26] and Gibson[27] have reported cases showing a temporary improvement over periods of two and three years respectively. It would be interesting to know the final outcome in these cases. In this connection it is pertinent to remark that Holboll's case died of the disease after showing some improvement over a period of five years.

Treatment. Every case of aplastic anemia demands a rigorous search for possible etiologic agents such as radium and benzol. Most of the cases reported during the past five years have been placed upon liver and liver extract, transfusions, and various forms of iron and arsenic therapy without success. A few cases were given arsphenamin injections but it is hard to see the rationale of this therapy as the drug is reported to be a cause of the disease in susceptible persons. In the case reported by Upham and Nelson improvement followed raw fetal liver feeding. From 400 to 1000 gm. were given daily. This case had failed to improve on raw liver, cooked fetal liver, and various forms of inorganic iron.

Gibson's case was not given liver. Improvement followed the daily subcutaneous injection of 5 minims of 1 to 1000 adrenalin. The therapy employed in both of the author's cases at the outset was hog's stomach extract in amounts as suggested by Sturgis for pernicious anemia. After a fortnight of failure, transfusion was resorted to as an emergency measure, and 3 minims of Fowler's solution were prescribed three times a day. On the twenty-fifth day stomach extract was discontinued, and 500 gm. of raw liver pulp was given daily. This was continued until shortly before the exitus. A capsule containing 30 grains of Blaud's mass and $\frac{1}{48}$ of a grain of copper (as carbonate) was given three times a day in addition to the raw liver without any evidence of bone-marrow stimulation. At the time the favorable results from raw fetal liver and adrenalin therapy were unknown to us. In view of the improvement reported, either or both of these should be given a trial.

Summary and Conclusions. Two cases of idiopathic aplastic anemia are reported:

The first case conforms clinically and pathologically with the majority of reported cases. The disease began with anemia; hemorrhagic phenomena and ulcerative stomatitis supervened; and at postmortem an extreme state of aplasia of the bone-marrow was found. All cellular elements of the blood were markedly reduced in number, the color index was above unity, and the predominating red cell was a macrocyte. Evidence of blood regeneration was

limited to the small percentage of reticulocytes which were constantly present.

In the second case the brunt of the attack was borne by the erythropoietic tissue. Platelet formation was not interfered with, while myeloid activity was little affected. The clinical course of the disease was therefore different from the ordinary case in that ulcerative stomatitis and hemorrhagic phenomena never made their appearance. The patient died as a result of the extreme anemia. As in the first case the color index was high and the modal erythrocyte was a macrocyte, but the polymorphonuclear leukocytes and the platelets were little affected. At no time was there any evidence of regeneration of red cells such as reticulocytes or nucleated forms. Both cases showed a normal fractional test-meal curve, a negative adrenalin test, and a progressively down-hill course to a fatal termination in spite of treatment by liver, stomach extract, and an iron-copper mixture.

The clinical and laboratory features of 17 authentic cases of aleukia hemorrhagica are reviewed. Cases occur in almost all age periods but are more common before the thirty-fifth year. More males than females are affected. The first symptoms are usually referable to anemia though many first sought treatment for bleeding from the nose or gums. Death usually results from extreme anemia but cases may die from excessive bleeding or from hemorrhage into the brain. The spleen and liver are rarely ever enlarged. The free hydrochloric acid in the stomach contents is retained, and cord changes do not occur. The features of the blood examination are profound anemia with high color index, a large red cell, a thrombopenia, and an absolute reduction in the number of polymorphonuclear leukocytes. Other features such as prolonged bleeding time, nonretractility of the clot, positive Rumpel-Leede test, depend upon the degree of thrombopenia, which is commonly such as to render them positive.

The differential diagnosis of the disease from aleukemic lymphosis cannot always be made with certainty during life.

The average duration of the disease is eight months, but often it is less than three months. Even temporary improvement rarely if ever occurs.

Treatment by raw fetal liver and adrenalin offers the best chance for temporary improvement.

Pathologically the features are profound anemia, generalized hemorrhages, and a fatty atrophic bone marrow. Small areas of myeloid and erythrocyte activity may be found, but megakaryocytes are seldom present. Necrotic ulcers are commonly found in the mouth and much more rarely in the large bowel. The liver, spleen, and lymphatic tissue are usually not remarkable.

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IDIOPATHIC NEUTROPENIA.

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Our reason for this addition to the already voluminous literature on idiopathic neutropenia is five-fold: (1) To decry the name "agranulocytic angina;" (2) to show the dependence of stomatitis upon neutropenia; (3) to reëmphasize the fact that neutropenia precedes evidence of infection; (4) to report 4 cases which are illustrative of some features which are discussed; and (5) to present a new viewpoint concerning the pathogenesis of the syndrome.

The name "agranulocytic angina" probably has hindered the thorough understanding of the symptom complex which has been so designated. This name is doubly unfortunate because it gives

unwarranted prominence to an inconstant and nonspecific manifestation, namely angina, and because "agranulocytic" allows of many interpretations. Agranulocyte is a term originally used to designate a nongranular adult cell of myeloid origin (abnormal neutrophil) Schilling.[1] If we assume the derivation of agranulocytosis to be agranulocyte—*osis* it would mean an increased number of these very special abnormal neutrophils. On the other hand we may assume that the compound term is derived from *a*–granulocyte—*osis*, in which case it would mean an absence of increase in granulocytes, that is, a normal count. Neither of these meanings is generally accepted. In recent literature agranulocytosis means a decrease in cells of the myeloid series, but occasionally an author interprets it to mean an increase in lymphocytes or monocytes. The supply of hematologic terms is so abundant that there should be little excuse for choosing such an ambiguous one. We shall, therefore, speak of the symptom complex in question as idiopathic neutropenia, thus making it analogous to idiopathic aplastic anemia and idiopathic thrombocytopenia.

TABLE I.—SUMMARY OF CASES REPRESENTING DISEASES IN WHICH BOTH NEUTROPENIA AND STOMATITIS OCCUR.

Diagnosis.	Age.	Sex.	Race.	Erythrocytes in millions.	Thrombocytes.*	Lowest leukocyte count.	Lowest percentage neutrophils.	Lowest leukocytes (absolute numbers).†	Spirochetes and fusiform bacilli in mouth lesions.	Nature of mouth lesions.	References.
							per cent				
Arsphenamin poisoning	50	F	W	2.9	0	550	4	22	Pos.	Ulceration membrane necrosis	(2)
Radium paint poisoning	35	F	W	1.0	Few	760	20	176	Pos.	Ulceration necrosis	(4)
Trinitrotoluene poisoning	21	F	W	1.2	....	480	10	48	....	Hemorrhage	(6)
Chronic benzene poisoning	32	M	W	0.7	70,000	1,400	13	182	Pos.	Ulceration necrosis	(7)
Roentgen ray and radium	..	M	..	...	....	200	4	8	....	Ulceration membrane	(8)
Idiopathic aplastic anemia	22	F	W	1.0	0.2 per cent	1,400	5	150	Pos.	Ulceration necrosis	
Acute leukemia	28	M	W	0.9	Few	90,000	0	0	Pos.	Ulceration membrane necrosis	
Infectious mononucleosis	26	M	W	4.3	300,000	6,500	9	1845	Pos.	Ulceration membrane	
Idiopathic neutropenia	8	F	W	3.6	....	50	0	0	Pos.	Ulceration membrane necrosis	
Idiophathic neutropenia	24	F	W	3.6	0.5 per cent	300	0	0	Very few	One small ulcer	
Idiopathic neutropenia	55	F	W	3.1	0.3 per cent	1,600	3	126	Very few	Ulceration in cycles	
Idiopathic neutropenia	7	M	W	0.8	....	3,100	2	96	Pos.	Ulceration membrane necrosis	

* Normal thrombocytocrit reading is in 0.4 to 0.6 volume per cent.

† The lowest total leukocyte counts did not always coincide with the lowest percentage of neutrophils.

The dependence of stomatitis upon neutropenia is illustrated in Table I. This tabulation consists of typical case records of various diseases which show both neutropenia and stomatitis. Some of the cases have been taken from the literature and some from our own records. Numerous authors have described oral lesions in that type of arsphenamin poisoning which is characterized by destruction of the bone marrow.[2,3] Martland, Conlon and Knef[4] have observed neutropenia with stomatitis in poisoning by radium paint. Voegtlin, Hooper and Johnson[5] reported anemia, leukopenia and oral ulceration in dogs poisoned by trinitrotoluene. Panton[6] reported a series of cases of trinitrotoluene poisoning, a few of which showed neutropenia, and one, bleeding from the gums. One of us observed a case of benzene poisoning with neutropenia and a sore mouth.[7] Lovett[8] mentioned stomatitis in neutropenia produced by the Roentgen ray and radium. Krumbhaar[9] described mustard-gas poisoning with neutropenia, but the extensive mucous membrane lesions caused by the gas made it impossible to determine whether or not there were mouth lesions secondary to the blood changes. Phenylhydrazine and many other chemical substances, most of which contain a benzene ring, may cause neutropenia, but we can discover no adequate case reports in which mouth lesions are mentioned. The cases of idiopathic aplastic anemia, acute leukemia and infectious mononucleosis[10] which appear in Table I, were taken from the records of the University Hospital. Similar cases are quite numerous.

While the care of the mouth is important in any very ill patient, this is particularly true in typhoid fever, in which disease the mild neutropenia may enhance the vulnerability of the oral mucous membrane. In the same connection it is interesting to speculate on the possibility of a relationship between neutropenia and the chronic glossitis of pernicious anemia and sprue.

It cannot be said that the relationship between neutropenia and stomatitis is quantitative. It must be admitted, however, that a severe leukopenia, especially a neutropenia, is frequently associated with mouth lesions, probably because the oral cavity constantly harbors virulent organisms and its natural barriers are subjected to frequent insults.

Report of Cases. Case I.—M. S., a white school girl, aged eight years, was admitted to the University Hospital October 26, 1910. The following record was obtained by Dr. C. Van Epps, who had seen the patient repeatedly before her admission, and in whose service she was admitted to the hospital.

On October 8, 1910, the child's parents noted that she was pale, but fever and indisposition were not apparent until October 10. The following day slight enlargement of the cervical, axillary and inguinal lymph nodes and the spleen was observed. The Widal test was negative. On October 14, the child complained of a sore throat. Examination of the blood revealed: Hemoglobin, 90 per cent; erythrocytes, 3,660,000; leukocytes, 600; neutrophils, 5 per cent; lymphocytes, 89 per cent; monocytes, 5 per cent; basophils,

1 per cent. The Widal test was again negative. The child continued to complain of sore throat and hoarseness, and by October 16, she was not able to speak above a whisper. During this time there was a daily temperature of 101° F. A gray, foul-smelling membrane was blown from the right nostril on October 18. The fever subsided two days later but the patient complained of toothache and was still unable to speak aloud. The pharynx and larynx were red and swollen. There was no apparent change in her condition until October 26, when the larynx was found to be two-thirds covered by a white membrane and diphtheria-like organisms were found by culture. During the next five days, antitoxin (45,000 units) was given without effect. A blood culture remained sterile. The temperature increased gradually from 100° F. on October 26 to 105° F. on November 4. On the latter date, the sputum became blood-streaked and petechiæ appeared on the forearms. The high fever persisted and the patient's condition gradually became more critical until, on November 8, induration of the gum margins was noted. The following day there was a marked ulceromembranous stomatitis, with beginning jaundice and a leukocyte count of 50 per c.mm. Staphylococci were cultured from the blood and the blood serum agglutinated typhoid bacilli. Death occurred on November 9, 1910.

Necropsy revealed: (1) Necrotic stomatitis pharyngitis and laryngitis; (2) hyperplasia of all lymph nodes; (3) acute splenitis; (4) bronchopneumonia. Typhoid bacilli (method of identification not known) were obtained from the heart's blood, the spleen and the mesenteric lymph nodes. Diphtheria-like organisms were found in the lungs, and spirochetes and fusiform bacilli were very abundant in the mouth, larynx and bronchi. The femur was removed but unfortunately the bone marrow was not described, and the sections were not preserved.

Comment Case I. This case presents numerous interesting features. Occurring as it did twenty years ago, it was regarded as an example of infection with bone-marrow exhaustion (Türk[11]). It may not be possible to disprove such a contention but two circumstances in this connection are worthy of consideration. (1) The leukocyte count was only 600 per c.mm. two days after fever was discovered. One cannot say that there was an overwhelmingly virulent infection at the beginning of the illness because the patient lived thirty-two days. (2) Bone-marrow exhaustion might account for the loss of cells of myeloid origin but is a less likely explanation for the absolute decrease in circulating lymphocytes and monocytes.

The results of bacteriologic studies in this patient are like those in many similar cases reported in the literature. Blood cultures taken early have been sterile, while agonal and postmortem cultures have revealed a multiplicity of organisms. Such late blood cultures have not been sufficiently ignored, especially since the disease is characterized by an early breaking down of the normal protective mechanism.

Organisms thought to be typhoid bacilli were found in the blood and tissues of this patient after death, and a positive Widal (titer not reported) was obtained twenty-four hours before death. In view of the clinical course, the early sterile blood cultures and the absence of ulcers in the intestinal mucosa at necropsy, it is more than likely that the organism found was only a terminal invader.

Staphylococci were also obtained in a late blood culture but no one would contend that the clinical course was that of staphylococcus septicemia.

Diphtheria is unlikely because of the extensive necrosis and the entire lack of response to the antitoxin, which was given as soon as organisms resembling diphtheria bacilli were found in the cultures.

Spirochetes and fusiform bacilli were abundant, but these organisms make their appearance sooner or later in most lesions of the mouth, especially in those associated with blood disease.

CASE II.—J. C., a graduate nurse, of healthy appearance, aged twenty-four years, was admitted to the University Hospital December 5, 1929. During the previous twenty-four hours she had noted chilliness, malaise, backache and soreness in the neck. Two other nurses who were associated with this patient developed glandular fever (infectious mononucleosis) and were also admitted on December 5, 1929. A year before, Miss J. C. had had an acute upper respiratory infection with a temperature of 101.8° F. and 2500 leukocytes, 48 per cent of which were neutrophils. Physical examination on December 5, 1929, revealed nothing of importance except that the submaxillary lymph nodes were slightly enlarged and tender. The next day there was slight redness of the gum margins. A small ulcer appeared on the hard palate on the fifth day, but it soon healed. A mouth wash of diarsenol was employed. Stab wounds made to obtain blood for cell counting were followed by areas of induration and purplish discoloration with tissue necrosis but without pus formation. A similar area of superficial necrosis appeared on the right leg. Thrombosis of the left femoral vein was discovered on the sixth day of the disease.

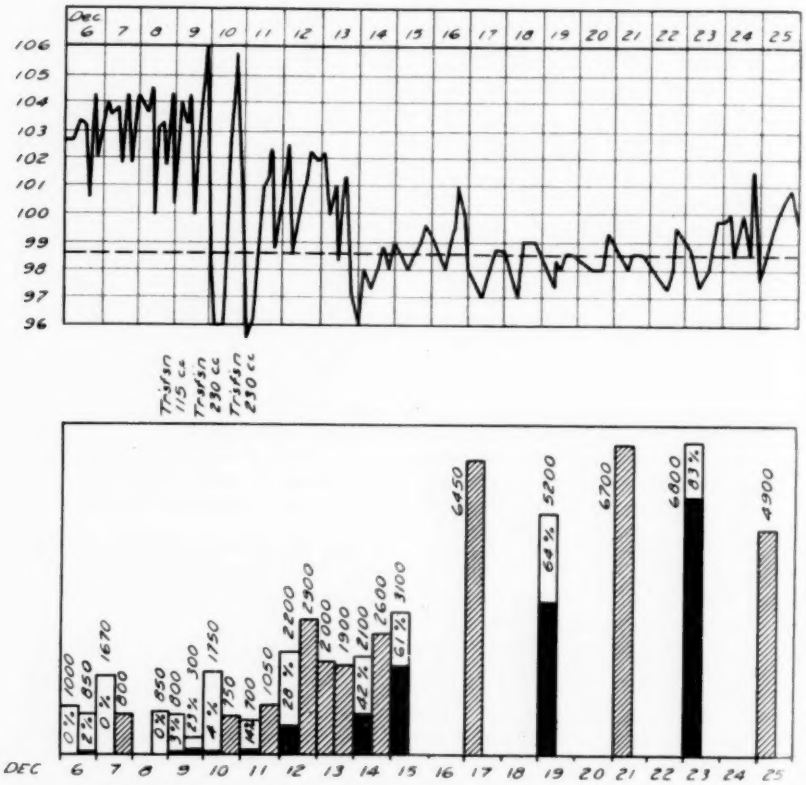
For nine days the patient was violently ill with chills, fever, sweats and prostration. At no time were the mouth lesions a prominent feature, and they might have escaped notice entirely had not attention been directed to them by the blood changes.

The temperature record and blood changes during the acute phase of the illness are shown in the chart on page 538. Four blood cultures were taken on different days. The first and fourth remained sterile but streptothrix grew in both the second and third.

The patient's convalescence was very protracted. After a month of rest, she still complained of feeling languid. Frequent examinations of the blood showed that the leukocytes ranged from 3850 to 7500 and the neutrophils varied from 26 to 72 per cent. Leukocytic extract and liver extract had no appreciable effect. On June 15, 1930, the patient suddenly developed swelling and redness of the eyelids and bridge of the nose. The lesion resembled facial erysipelas. There was very little fever but the leukocytes dropped from 5200 to 4350 and then to 3850 per c.mm., while the percentage of neutrophils increased from 26 to 66 per cent. After about five weeks the skin cleared, but a similar lesion appeared a week later and lasted five days. In September, 1930, three immunizing injections of triple typhoid vaccine were given. The leukocytes were counted before the injections and at two-hour intervals thereafter. Six hours after the third injection the leukocytes were 12,950 per c.mm. 78 per cent of which were neutrophils. A control patient showed 11,380 leukocytes with 90 per cent neutrophils.

Comment Case II. This case demonstrates two very important features of idiopathic neutropenia. Leukopenia was demonstrated a year before and for several months after the acute episode. The

stomatitis was trivial and did not appear until the second day of the illness. The unusually good mouth hygiene, which was habitual in this patient, may have accounted for the mild nature of the stomatitis. The organism found in the blood cultures was not virulent for animals. The association of this patient with two other nurses who developed glandular fever (infectious mononucleosis) is interesting, but does not warrant conclusions.



Unshaded portion represents mononuclear cells.
Black portion represents neutrophils.
Shaded portion represents leukocyte counts without differentials.

Temperature record and leukocyte counts during the acute phase of the illness in Case II.

CASE III.—Mrs. L. J., aged fifty-five years, was examined at the University Hospital March 4, 1926, by Dr. F. J. Rohner. The very long and eventful history is as follows: She had never been strong but had been active until the summer of 1921. At this time she became listless and after a few weeks, a pyelitis was discovered. Under treatment the pyelitis improved very slowly, but the listlessness continued. After a year of poor health, she developed "dirty yellow ulcers" in the mouth. These ulcers

appeared every five or six weeks for the next four years, and were often associated with red maculæ on the skin. The mouth ulcers varied from 0.5 cm. to 3 cm. in diameter and the skin lesions were about 0.5 cm. in diameter. When first examined March 4, 1926, the leukocytes numbered 7800 per c.mm. and no cause for the sore mouth could be found. In the summer of 1926 her left hand was badly lacerated. The wound required months to heal, even though there was little pus formation. About this time it was discovered that the patient was having irregularly recurring periods of fever lasting three or four days. She felt certain that these periods of fever had existed for months previously. The next three years were spent in a vain effort to find the cause of the fever, which became very regular in its cycles. The temperature would increase gradually to about 104° F. and then slowly subside. The febrile periods were three or four days long, and the afebrile intervals varied from three to ten days in length. The cycles of fever were unaffected by a tonsillectomy, and various sinus operations. Because of the discovery of an area of increased density in the hilum of the right lung, the patient spent several months in Colorado. Finally, on March 25, 1929, she was readmitted to the University Hospital. Examination revealed an enlarged spleen and the same monotonous cycles of fever. Blood cultures, agglutination tests for undulant fever, typhoid fever, paratyphoid fever and tularemia were repeatedly negative. Malarial parasites could not be found and the Wassermann test was negative. Roentgen ray films of the chest showed some scars in both upper lobes but neither the symptoms nor physical signs suggested active tuberculosis of the lungs. Quinin and neoarsphenamin did not affect the fever and liver extract over a long period did not change the blood picture.

In September, 1929, the patient became depressed and in October she was admitted to the Psychopathic Division. In December a mastoidectomy was done on the left side. Pus containing hemolytic streptococci was obtained from beneath the periosteum and from the mastoid cells. During February and March, 1930, the patient had three attacks of what appeared to be a very chronic facial erysipelas. She finally developed diarrhea and a marked dermatitis of the hands, which led to a diagnosis of pellagra.

At this point such diagnoses as Hodgkin's disease with Pel-Ebstein type of fever, aleukemic leukemia and tropical diseases became definitely untenable. We were forced to the belief that the patient had a chronic leukopoietic insufficiency and that the various infectious manifestations were secondary. Splenectomy was done (April 22, 1930) in the hope of provoking a beneficial leukocytosis, but although the usual platelet response occurred, the postsplenectomy leukocytosis was not very significant (see Table II) and had no appreciable effect on the course of the disease. Bed sores which had bee resent for months, continued to increase in size and depth. The patient died May 27, 1930.

The spleen weighed 480 gm. The Malpighian corpuscles were largely replaced by amyloid. There was no myeloid metaplasia and only moderate increase in fibrous tissue.

Necropsy revealed: (1) Extensive decubital ulcers; (2) mastoiditis with extensive osteomyelitis, right; (3) streptococcic peritonitis; (4) amyloidosis of the liver, kidneys and adrenals; (5) hyperplasia of the bone marrow.

The postmortem blood cultures and cultures from the right mastoid showed bacillus coli. A hemolytic streptococcus was obtained from the peritoneal cavity. A great variety of organisms was found in the middle ears and in the decubital ulcers. The paranasal sinuses were clean and cultures from them remained sterile.

The most remarkable finding at necropsy was the hyperplastic bone marrow. The shaft of the femur and the ribs contained a gray cellular marrow. Microscopically the femur marrow showed very few nucleated

erythrocytes or adult neutrophils. There was an occasional eosinophilic leukocyte and large numbers of both myelocytes and myeloblasts. In smears of the bone marrow (Isaac's method)[2] myelocytes (many eosinophilic) and myeloblasts were very numerous, and of normal appearance. The marrow of the rib contained more erythrocytic elements than that of the femur.

TABLE II.—SUMMARY OF THE BLOOD DATA IN CASE III.

	Red blood cells.	White blood cells.	Pn.	Mononuclears.	Platelets, %.	
March 4, 1926	....	7800				
July 7, 1927	....	3600				
Mar. 20, 1929	4,800,000	2100				
Mar. 23, 1929	3,936,000	2000	16	84		
Mar. 25, 1929	....	2100	..	..	0.2	
April 4, 1929	....	1600				
April 7, 1929	....	1850				
April 29, 1929	....	2600				
May 15, 1929	....	1600				
May 19, 1929	....	2200				
Oct. 28, 1929	3,150,000	6650	11	89		
Feb. 21, 1930	4,160,000	1750	14	86		
Feb. 23, 1930	....	2400				
Mar. 10, 1930	....	4200	3	97		
Mar. 25, 1930	....	4900				
April 10, 1930	4,600,000	3600				
April 19, 1930	4,030,000	2200	42	58	0.3	splenectomy (4-22-30)
April 23, 1930	....	4100	37	63	0.4	
April 24, 1930	....	4800	43	57	0.6	
April 25, 1930	....	2900	45	55	0.6	
April 26, 1930	....	2500	40	60	0.85	
April 27, 1930	....	3900	19	81	1.0	
April 28, 1930	....	3700	40	60	1.0	
April 29, 1930	....	4300	42	58	1.1	
May 2, 1930	....	7800	23	77	1.3	
May 4, 1930	....	5550	40	60	1.1	
May 6, 1930	....	8650	59	41	1.1	
May 8, 1930	....	4200	45	55	1.1	
May 10, 1930	....	4450	48	52	1.1	
May 15, 1930	....	5400	48	52	0.8	

No myelocytes were found in the circulating blood. Metamyelocytes were present at times but never made up more than 4% of the total number of leukocytes. Stab forms were constantly present and on three occasions before splenectomy the neutrophils were all of this type. Segmented forms increased in number after splenectomy but many of these cells showed vacuoles in the cytoplasm and variation in the size and staining reaction of the granules.

During life several oxidase stains were made on the blood and each time it was found that the neutrophils contained little or no peroxidase ferment. The same stain was applied to the bone marrow smears and even the well developed myelocytes with large granules, did not give a peroxidase reaction. The significance of this finding which is also mentioned by Schilling, is not understood.

Comment Case III. The chronicity and the periodicity were the most remarkable features in Case III. Unfortunately, neutropenia was not proved during the first five years of her illness. From

1922 to 1926 the disease was characterized by recurrent attacks of sore mouth, a manifestation which was absent during the succeeding four years. During the nine years that the patient was ill, she was beset with a multiplicity of unrelated types of sepsis. Her enfeebled protective mechanism no doubt varied in efficiency, and the organisms which she harbored varied in virulence, but these chance variations are not sufficient to explain the remarkable periodicity of the mouth lesions and the fever.

The bone marrow in this case was not like that of most of the acute cases described in the literature. In an occasional case of long duration some myeloid hyperplasia has been found.[13] The overgrowth of myelocytes and myeloblasts in our case was almost as marked as in myelogenous leukemia. It is unfortunate that a biopsy of the bone marrow was not obtained before splenectomy, because it is the only means by which we might have determined the part played by the splenectomy in this overgrowth of myeloid cells.

CASE IV.—D. C., a white American boy, aged seven years, was admitted to the University Hospital February 9, 1930. During the winter of 1929–1930 he lost some weight and appeared slightly pale but did not complain, and continued in school. About noon, January 29, 1930, he complained of sore throat which was quickly followed by a chill, fever and sweating. The fever continued but he complained only of a headache. On February 5 there was bleeding from the gums, and on February 7 a loose tooth was extracted. Bleeding from the gums continued and a quantity of changed blood was vomited.

Examination on February 9 revealed a very pale but well-developed child. The lymph nodes at the angles of the jaw were 2 cm. in diameter, soft and tender. Other lymph nodes and the spleen were not enlarged. The tonsils were enlarged and there was a dirty, gray membrane over the left tonsil. An old ecchymosis in the right groin was attributed to a bruise. No other physical abnormalities were discovered. Examination of the blood showed hemoglobin, 25 per cent; erythrocytes, 830,000; leukocytes, 3100, of which 8 per cent were neutrophils, 81 per cent lymphocytes, 8 per cent unclassified (not blast cells) and 4 per cent shadow cells. Thrombocytes were very scarce in the smear. The blood Wassermann was negative. A blood culture taken on admission remained sterile. Bacillus coli grew in a blood culture taken two days before death. The average temperature was about 104° and was quite constant except following transfusions, when, on one occasion, it dropped abruptly from 107.8° to 97.4° F. Eight blood transfusions, averaging 150 cc. each, were given. The erythrocytes increased to 2,150,000 but the leukocytes never exceeded 4800 per c.mm. The neutrophils varied from 8 per cent on admission to 2 per cent before death. The gum margins continued to bleed and the throat gradually became gangrenous. The throat was treated locally with diarsenol without effect. The patient died February 22, 1930.

The findings at *necropsy* were: (1) Extensive gangrene of the mouth and pharynx; (2) acute splenic tumor; (3) relatively aplastic bone marrow. The bone marrow contained numerous nucleated erythrocytes, some myelocytes, a few neutrophils and numerous small mononuclear cells. Megakaryocytes were rare. There was no leukemic infiltration of the viscera.

Comment Case IV. The interesting features in Case IV are the anemia and the hemorrhages. Leuchtenberger[14] would classify this case as agranulocytosis complicated by anemia and hemorrhagic diathesis. It is difficult, if not impossible, to differentiate such a case as this from poisoning by benzene, or from the idiopathic type of aplastic anemia. It is noteworthy that this child who weighed 18.7 kg. was given 1200 cc. of blood which increased the erythrocytes 1.3 million per c.mm., yet there was an actual decrease in neutrophils from 248 to 90 per c.mm. Such an occurrence is not peculiar to idiopathic neutropenia.

Discussion. Without meaning to belittle the many excellent reports in the literature, we believe that the obvious tendency to consider "agranulocytic angina" as a septic disease is unfortunate. Further progress toward an understanding of the syndrome would be promoted by the reports of unusual instances, and the long continued observation of acute nonfatal cases. Hueper[15] states, "Essential agranulocytosis (Schultz) can be differentiated by its clinical and pathological symptoms from diseases showing a secondary agranulocytic symptom complex." In a rather limited number of cases which fulfill all of the requirements originally laid down by Schultz, this statement seems to obtain, but borderline cases are numerous. A few authors insist that normal numbers of circulating erythrocytes and thrombocytes are essential to the diagnosis. Zadek[16] feels that a virus of sufficient potency to so completely destroy the myelocytic apparatus could not uniformly spare all of the closely related neighboring cells. A review of the literature shows that neutropenia and necrosis of tissue are the only manifestations which are common to every case. The septic lesions of this condition we believe to be incidental and secondary. The necrosis of tissue however, may be an important and fundamental manifestation.

Bickel[17] has discussed the similarity between agranulocytosis and aleukemic leukemia. This relationship may be very intimate. We have recently seen three children under seven years of age, with gangrenous stomatitis, high fever, leukopenia, almost complete neutropenia with no young circulating cells, marked anemia, thrombocytopenia and enlargement of the liver, spleen and lymph nodes. These children died but necropsies were not permitted. The criteria which differentiate aleukemic leukemia from idiopathic neutropenia are, the abnormal circulating cells, the hyperplastic bone marrow, and the presence of leukemic infiltration in the viscera. These points need careful elaboration, especially in view of the hyperplastic bone marrow in Case III, and since some authors have observed myeloblasts and myelocytes in the circulating blood during recovery from attacks of neutropenia. In Bickel's case there was leukemic infiltration of the viscera, with a fatty bone marrow and a nonleukemic blood picture. In cases such as these the diagnosis is apt

to be a matter of personal opinion. Much the same might be said of Case IV.

Weiss[18] differentiates "agranulocytosis" from lymphatic reaction by the fact that in the latter there is an absolute increase in lymphocytes which replace the neutrophils to make the total leukocyte count normal or increased. It might be added that in lymphatic reaction there are usually many abnormal lymphoid cells while in idiopathic neutropenia most of the lymphocytes are normal. Many authors do not accept as "agranulocytosis" any case in which there is a significant absolute increase in lymphocytes or monocytes. Such rules are of doubtful value. The question of a relationship between idiopathic neutropenia and infectious mononucleosis should remain open. The contact of Case II with two other patients who developed glandular fever (infectious mononucleosis) is noteworthy. We have seen one patient with infectious mononucleosis in whom the circulating neutrophils completely disappeared. The clinical manifestations in this patient, however, were much more benign than those of idiopathic neutropenia. It is possible, but not likely, that the difference between idiopathic neutropenia and infectious mononucleosis is merely a difference of degree.

Aplastic anemia, in addition to the aplasia of the erythrocytic elements, usually includes leukopenia, especially neutropenia, as well as thrombocytopenia (Aleukia). Certain cases called "complicated agranulocytosis" by Leuchtenberger[14] resemble aplastic anemia. The infectious manifestations may be similar[19] in the two diseases except that in aplastic anemia the onset of the fever is usually not so abrupt. Idiopathic neutropenia and aplastic anemia both show a severe neutropenia, the cause of which has been determined in some varieties of aplastic anemia. Benzene, neoarsphenamin, radium paint, trinitrotoluene, Roentgen ray and phenylhydrazin all cause neutropenia but they also cause an aplastic type of anemia and thrombocytopenia. Is it not possible that some chemical substance might destroy the granulocytic apparatus without damage to the other bone-marrow elements?

Those hematologists who feel that agranulocytic angina is the result of bone-marrow exhaustion by nonspecific sepsis will interpret the blood picture as being an extreme shift to the left. In the case reported by Roberts and Kracke[20] there was a tendency toward a shift to the left at the onset of the second attack. One of Zadek's[16] patients (Case IV) also developed a leukopenia under observation but the two complete differential studies which are reported do not show a shift to the left. The patient also developed anemia and thrombocytopenia. The profound neutropenia which some patients show before they are symptomatically ill speaks most eloquently against idiopathic neutropenia being only a shift to the left, with eventual exhaustion. This is best demonstrated by Roberts' and Kracke's case.

Thrombocytopenic purpura presents no great clinical similarity to idiopathic neutropenia. The hemorrhagic manifestations which are observed in the latter are likely due to a terminal septicemia rather than a lack of blood platelets. However, the two conditions present an interesting analogy in that in each there is a selective depression of one blood element often without effect upon other circulating components. Both are more common in women. Removal of the spleen, which is followed by an increase in both platelets and leukocytes, is often curative in thrombocytopenic purpura. In our case of neutropenia, in which splenectomy was done, there was a definite increase in thrombocytes, though not the enormous increase which follows splenectomy in Banti's syndrome or in hemolytic icterus. Although the postsplenectomy increase in circulating leukocytes was slight, a marked overgrowth of young myeloid cells was found in the bone marrow at necropsy thirty-five days after splenectomy.

While the evidence at hand does not permit of definite conclusions as to the etiology and pathogenesis of idiopathic neutropenia, it does cast doubt upon certain theories which have been advanced.

Exhaustion of a normal bone marrow as the result of nonspecific sepsis has been eliminated from consideration by the very fundamental observations of Roberts and Kracke. These authors have definitely demonstrated that the neutropenia precedes all evidences of infection.

Infection by an organism, the virus of which has a specific affinity for the granulocytic system, was suggested by Lovett.[8] The experimental work which has been done on guinea pigs is not conclusive because the leukocytes of guinea pigs are most variable in their behavior, and neutropenia has been obtained in these animals with organisms other than bacillus pyocyaneus.[21]

A third suggested explanation of the neutropenia, *viz.*, infection of the bone marrow *per se*, has never been observed except in terminal septicemia.

"Paralysis of the bone marrow" implies a neurologic lesion. Until it can be demonstrated that bone-marrow activity is regulated by a nervous mechanism, this explanation is not justified.

Many years ago neutropenia was attributed to negative chemotaxis. Some such vaguely understood mechanism is to be considered in typhoid fever and infectious mononucleosis because in these diseases the injection of foreign protein will result in an increase in circulating neutrophils.[10] Negative chemotaxis in the ordinary sense need not be considered in idiopathic neutropenia because in the acute stage of this disease the bone marrow is depleted of myeloid cells.

Chemical poisoning of the granulocytic apparatus is certainly possible, but we are not aware that any drug acts solely on the myeloid tissue.

A congenital hemopoietic insufficiency is a possible explanation. Hart[23] has observed fatal idiopathic neutropenia in two sisters. A familial tendency is also suggested by Bickel.[17] One of our patients (Case II) is known to have had a leukopenia during an infection a year before she developed idiopathic neutropenia, and the patient reported by Roberts and Kracke had a definite relative lymphocytosis five and a half years before the acute episode developed. Both of these patients continued to show a moderate neutropenia after recovery from the first attack. In another of our patients (Case III) there was a constant severe neutropenia for three years (probably nine years) during which time she suffered from many acute and chronic infections. Somewhat similar cases are reported by Rutledge and others and by Paroulek,[24] the former case being particularly suggestive of a congenital anomaly. In several of the reported cases there have been repeated acute attacks. In 2 cases[20,24] myelocytes and myeloblasts entered the circulation in large numbers during recovery. Even if we consider the strain on the bone marrow, these reactions were unusual and might suggest a congenital weakness.

Against a congenital hemopoietic insufficiency we have several arguments, most of which are as intangible as those which favor it. In most patients idiopathic neutropenia develops in later life after many years of apparently normal existence. Also the cyclic nature of the condition is hard to explain on the basis of a congenital lesion, though Rutledge and others, suggest that it may be dependent upon some anomaly of the glands of internal secretion. Blumer[25] dismisses the possibility of a congenital anomaly with the following statement, ". . . the same patient has reacted with the usual polymorphonuclear increase to one attack of an infection and has shown an agranulocytic reaction to another attack." While this statement may be correct, we can find no case in the literature which fully justifies all of its implications. Blumer (personal communication) saw a patient who had 7200 leukocytes with 72 per cent neutrophils during an attack of tonsillitis less than five months before the onset of idiopathic neutropenia. It is to be recalled that one of our patients (Case II) responded to typhoid vaccine with a slight neutrophilia. The real truth as to the adequacy of the bone marrow in these cases cannot be determined until someone observes a patient with idiopathic neutropenia in whom there develops a separate disease such as empyema which requires the very rapid elaboration of huge quantities of neutrophils. Adequate proof of a very marked leukocytic reaction to infection would preclude the possibility of a congenital hemopoietic insufficiency if it preceded an attack of idiopathic neutropenia, and would prove that the bone marrow had not been permanently enfeebled if it occurred subsequently.

At this time we must take cognizance of a viewpoint concerning the pathogenesis of idiopathic neutropenia which is much more

subtle than any of those previously mentioned. We have stated that neutropenia and tissue necrosis are constant features probably of primary importance. The necrosis may be due to local tissue reactivity, anaphylactic or otherwise. Schilling has demonstrated neutropenia in anaphylaxis[1] (p. 197). Roberts and Kracke emphasized the fact that exactly the same area on the tongue became necrotic in both of the attacks which their patient suffered. Might not this necrosis be the result of local tissue reactivity? One of us observed a patient with Arthus phenomenon,[26] following the injection of diphtheria antitoxin, in whom there were definite exacerbations and remission in the local and general symptoms. In this patient each injection of antitoxin was followed by a fall in the leukocyte count, once from 18,000 to 13,700, and on the second occasion from 16,800 to 10,400, but differential counts were not done. In the case reported by Rutledge and others, there occurred an eosinophilia with each attack, a feature which also suggests anaphylaxis. Shwartzman[27] has recently described a local tissue reaction which is somewhat similar to the Arthus phenomenon, but differs from it in certain respects. The injection of a bacterial filtrate is an essential feature of the "Shwartzman reaction." A local area is prepared by the subcutaneous injection of the filtrate and the reaction occurs in this area upon the intravenous injection of more filtrate twenty-four hours later. Talley, in discussing the paper of Roberts and Kracke, mentioned the fact that Eiman had suggested a possible relationship between the "Shwartzman reaction" and idiopathic neutropenia. As far as we can determine, neutropenia, periodicity and eosinophilia have not been observed in connection with the "Shwartzman reaction." If this reaction were the one which takes place in idiopathic neutropenia the site of necrosis would be determined by the point at which the offending material was absorbed during the first vaccination. If, on the other hand, it be the Arthus phenomenon which takes place, the necrosis would occur at the site from which the protein was absorbed last. In either case the offending material would likely be of bacterial origin and in most instances would gain entrance to the body through the mucous membranes of the alimentary or respiratory tracts. This idea as to the pathogenesis of idiopathic neutropenia might account for the neutropenia, the necrosis, the periodicity, the acute onset and the occasional eosinophilia, but is somewhat discredited by the late appearance of the necrosis and the occurrence of similar necrotic lesions in many other diseases which are characterized by neutropenia.

Certainly further investigation of this interesting symptom complex is needed.

Summary and Conclusions.—1. The name "agranulocytic angina" is unfortunate because of its intrinsic ambiguity, and because it implies that we are dealing with a mouth infection which causes

neutropenia instead of with a syndrome of utterly unknown etiology and pathogenesis.

2. Stomatitis is such a common secondary manifestation in the blood dyscrasias which are characterized by neutropenia that it is probably of no etiologic importance.

3. From a study of our own cases we concluded that neutropenia was primary and infection secondary, an idea which found final proof in the case reported by Roberts and Kracke.

4. In view of the inadequacy of our present knowledge we feel that it is not justifiable to divide the syndrome arbitrarily, and suggest that all cases of unexplained neutropenia with secondary infection be grouped under the general head of idiopathic neutropenia.

5. The similarity between aplastic anemia, aleukemic leukemia and idiopathic neutropenia (especially the complicated forms) is emphasized.

6. We have included the record of a patient who was in the University Hospital in 1910 to illustrate the fact that in former years idiopathic neutropenia was either overlooked because the blood was not examined, or was interpreted as a symptom of bone-marrow exhaustion, aleukemic leukemia or aplastic anemia.

7. Splenectomy was performed in one of our cases with no apparent benefit.

8. The similarities which idiopathic neutropenia bears to anaphylaxis and the Shwartzman reaction are discussed.

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MESENTERIC SMALL VESSEL SCLEROSIS WITH ULCERATION AND GANGRENE OF THE ENTERIC TRACT.

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A careful search of the available literature fails to reveal any cases of gangrene or ulceration of the enteric tract attributed to atherosclerosis of the smaller arteries. In 1927, Leitman described a case of massive gangrene of the lower portion of the ileum and the upper extent of the colon, which he ascribed to far-advanced atherosclerosis of the superior and inferior mesenteric arteries with almost complete occlusion by large plaques. He made no mention of the smaller vessels. Most of the cases on record of massive gangrene of the enteric tract are associated with embolism or septic thrombosis.

In 1925, Dow published a statistical study of the incidence of atherosclerosis of the various arteries of the body. He said, "A very

prominent feature of my analysis was the comparative freedom from atheroma of the greater part of the main stem of the mesenteric vessels and the branches into which they divided."

The clinical syndrome in abdominal arteriosclerosis is usually discussed under the term "Angina Abdominalis." This term was first used by Baccelli. In 1928, Gauss reviewed this subject, defining abdominal angina as "a symptom complex, secondary to cardiovascular disease, occurring usually in persons past forty with arteriosclerosis, characterized by abdominal pain which tends to be severe, paroxysmal and recurring; it is associated with general weakness, loss of weight, and frequently, abdominal distention and belching." Men are more frequently affected than women.

Held, in 1925, stated that "localized repeated vasoconstriction of the gastric vessels, especially those supplying the submucosa, may lead to gastric erosion and even to ulcer formation."

At the Cincinnati General Hospital there have recently come under observation 2 cases of massive gangrene, and one of extensive ulceration, of the enteric tract, associated with sclerosis of the smaller mesenteric vessels.

Case Reports.—Case I (N–30–221). The patient was a white woman, aged sixty-one years, admitted to the hospital March 11, 1930, with the complaint of persistent cough accompanied by shortness of breath and palpitation. The family history was essentially negative. Several years before, the patient had an attack of rheumatism, following which a diagnosis of "rheumatic fever with cardiac involvement" was made. For the five years previous to admission the patient had gradually become more dyspneic and during the last year had developed edema and palpitation. There had been some loss of weight. No history of any gastroenteric disturbance was obtained.

The significant findings of the *physical examination* were: marked cyanosis; emphysematous chest; loud systolic murmur over the precordium with irregular premature contractions; blood pressure of 174 systolic and 120 diastolic; marked sclerosis of the peripheral vessels; distended abdomen with shifting dullness; pitting edema and cyanosis of the lower extremities. The Wassermann reaction was negative. There was a slight leukocytosis (10,000), and the urine showed 3+ albumin. A teleoroentgenogram revealed cardiac enlargement, accompanied by chronic pleurisy and pleural effusion. The patient did not tolerate digitalis or diuretics and her dyspnea was only slightly relieved by morphin. The blood pressure changed to 190 systolic and 105 diastolic. She vomited frequently. Auricular fibrillation began and the cyanosis became more pronounced. The urinary output became markedly diminished and the edema increased. One month after admission the patient died with the diagnosis of cardiac decompensation.

At autopsy, the heart weighed 475 gm. Ball thrombi, were found attached lightly to the lining of the right atrium over areas of myocardial infarction. Portions of these thrombi were found plugging two large branches of the pulmonary arteries, with resultant pulmonary infarction. The mitral valve measured only 70 mm. in circumference and revealed evidence of old rheumatic and atherosclerotic disease. Atheromatous patches and plaques were found in the large coronary arteries, in the aorta and its large branches and in the pulmonary vessels. The most conspicuous feature on superficial examination of the abdominal organs was extensive discoloration of the

gastroenteric tract, most marked in the transverse colon. The color varied from a reddish purple to a purplish black. The entire tract was moderately distended without any evidence of obstruction or perforation. After opening the bowel the only portions not involved in the gangrenous process were found to be the rectum, the lower half of the sigmoid and a small portion of the ileum just above the ileocecal valve, these portions being sharply demarcated from the gangrenous parts. A careful examination of the larger mesenteric vessels revealed slight thickening only in the celiac axis. Microscopic sections showed marked sclerosis of the small arteries and arterioles in the mucosa and submucosa of the gastroenteric tract. The areas supplied by these vessels were extensively necrotic, with diffuse infiltration of polymorphonuclear leukocytes. In the submucosa, the process resembled a diffuse cellulitis with marked edema of the tissues, while more superficially the lesion was similar to that of anemic infarction. Microscopic examination of sections from other viscera revealed a moderate atherosclerosis of both large and small vessels.

The pathologic diagnoses were: far advanced chronic rheumatic and arteriosclerotic heart disease with mitral stenosis, atrial thrombosis and pulmonary infarction; small vessel atherosclerosis in the gastroenteric tract with mucosal and submucosal gangrene; generalized arteriosclerosis and arteriolosclerosis with scarring of the kidneys; generalized edema and chronic passive congestion of the viscera; pulmonary emphysema.

Case II.—(N–30–304). The patient was a white man, aged forty-one years, admitted to the hospital April 9, 1930, complaining of occasional dull pains in the left leg, left hip and rectum, of about three weeks' duration. The family history was essentially negative. The past history included measles, chickenpox, pertussis, typhoid fever and malaria. The patient stated that he had had no gastroenteric disturbances, except constipation, the last bowel movement having been five days before admission.

Physical examination revealed an emaciated but fairly well-developed man apparently not acutely ill. Examination of the chest was essentially negative. The blood pressure was 102 systolic and 66 diastolic. Examination of the abdomen revealed very poor relaxation and elicited a sense of resistance in the right upper quadrant. On rectal examination, internal hemorrhoids were palpated. Two days after admission, an enema was given, following which a large amount of fecal material was passed. During the next ten days there was no bowel movement. The patient's condition continued unchanged except for considerable abdominal pain during attempts at defecation. Proctoscopic examination was negative. There was a leukocytosis of 13,000. The urine, spinal fluid Wassermann and neurologic examinations were essentially negative. A barium enema appeared to remain entirely in the colon so the possibility of enteric neoplasm was considered. Three weeks after admission, the proctoscopic examination was repeated without positive findings. During the same day the patient had an attack of severe pain in the abdomen accompanied by indefinite patterns, not motile, on the left side. At this time a small indefinite mass was felt in the left lower quadrant but there was no abdominal rigidity. Two days later the patient became nauseated and vomited and there was a definitely palpable mass just above the left iliac spine. Five days after this a dark red bloodclot was passed per rectum. The patient was transferred to the surgical service and an exploratory laparotomy was performed. The mass in the left lower quadrant was found to be a very hard fecolith impacted in the colon. In the small intestine there were several areas of discoloration suggesting recent intestinal obstruction. The stasis may have been partially relieved by the pre-operative enema. The day following the operation, the patient began developing edema and his condition became

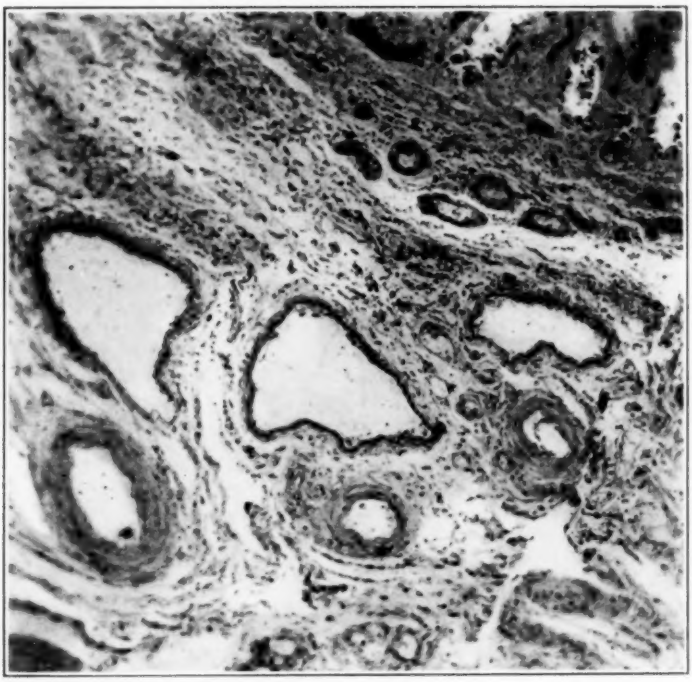

FIG. 1.—Case I. N–30–221 Sclerosis of arterioles in the intestine with early gangrene of the mucosa.

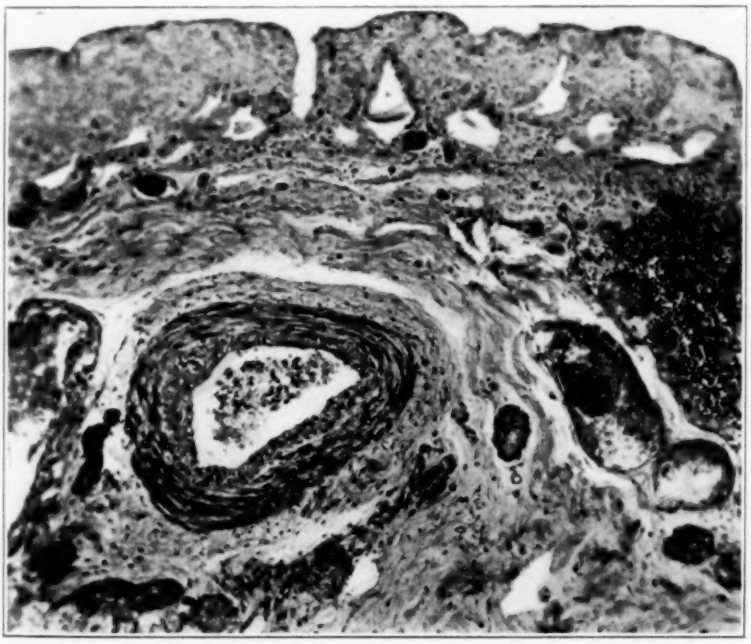

FIG. 2.—Case III. N–30–404. Sclerosis of small arteries in the intestine.

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very poor. Two days after operation the patient vomited and pulmonary edema became marked. Three days later the patient died suddenly, having had no bowel movements following the laparotomy.

At autopsy, a considerable amount of blood was found in and about the abdominal wound to which a loop of ileum was bound by fibrinous adhesions. On opening this portion of the intestine a large area of ulceration was encountered, fairly well marked off from the surrounding normal portions of the bowel. Several similar ulcers were found in other portions of the ileum, jejunum, cecum and colon. There were also a number of serpiginous ulcers, situated on the lesser curvature of the stomach near the pylorus, possessing slightly thickened edges and shallow centers. All of these ulcers contained white plastic exudate and were very distinctly outlined. The surface of the ulcers was coated with fecal material which could not be washed off readily.

The heart weighed 365 gm. The musculature was soft and sticky with a cooked appearance, and on section presented numerous fibrotic areas, some of which had soft, red centers. The coronary arteries contained numerous atheromatous patches, and in the left anterior descending branch there was a fresh thrombotic mass completely occluding the lumen. The aorta and its larger branches contained very few atheromatous areas and showed only a slight decrease in elasticity. Similar changes were found in the pulmonary arteries. The large mesenteric vessels were not remarkable.

Microscopic examination revealed extensive scarring of the smaller vessels related to the ulcerated areas of the enteric tract. The ulcers consisted of eroded mucosa infiltrated with polymorphonuclear leukocytes, beneath which extensive granulation tissue was present. In some of the ulcers there was complete loss of structural outlines in the mucosa and submucosa. In others, the gangrenous process extended through the entire wall and involved the serosa. There was moderate arteriosclerosis in the other viscera and very marked scarring and thrombosis of the coronary vessels.

The *pathologic diagnoses* were: far-advanced coronary sclerosis with thrombotic occlusion and extensive myocardial degeneration; focal small vessel sclerosis in the gastroenteric tract with chronic and acute ulceration; moderate generalized arteriosclerosis; subacute and chronic interstitial pancreatitis; early cirrhosis of the liver; chronic cholecystitis and cholelithiasis; prostatitis with small adenomata in the prostate and kidney; acute bronchitis; pulmonary edema and emphysema; toxic changes in the viscera.

Case III.—(N-30-404). The patient was a colored male, aged fifty-seven years, admitted to the hospital March 5, 1930, complaining of dropsy. The patient's history was unreliable. He stated that he had been in good health until his present illness. He had had gonorrhea and several penile lesions while a young man. His wife died in childbirth but there are two healthy children. The onset of the present illness was two years before, with dyspnea and a slight cough. The edema of the lower extremities had become much worse within the last two months. He had been vomiting every morning but believed this to be caused by a medicine prescribed by an outside physician. There was no history of any other gastroenteric disturbance. The patient stated that he had had rheumatism. The physical findings were: Cheyne-Stokes respiration; emaciation that suggested a recent loss of weight; sluggish pupils; pulmonary emphysema and congestion; marked enlargement of the heart downward and to the left, with a diastolic murmur audible over the aortic area and the entire left side of the sternum. The peripheral vessels were tortuous and sclerotic and the pulse was Corrigan in type. The heart was regular in rhythm but variable in rate. During hypernea the rate dropped to about 48. During apnea it varied between

66 and 72. The abdomen moved freely with respiration. The liver and spleen were not palpable. There was only a slight pitting edema of the lower extremities. The blood pressure was 210 systolic and 50 diastolic. The Wassermann was strongly positive. The urine showed 1+ albumin on one occasion. The blood, spinal fluid and blood chemistry were not remarkable. A teleoroentgenogram revealed marked cardiac enlargement to the left. The patient improved under antisyphilitic treatment and was discharged on April 12, 1930, but was told to continue treatment at the cardiac clinic. The patient returned to the hospital two months later with substernal pain in addition to the previous complaints. He also stated that he had been constipated. The physical findings were essentially the same as on the previous admission except that the evidences of cardiac decompensation were more marked. The blood pressure had risen to 250 systolic and 70 diastolic. Two weeks later the patient became comatose, but gradually recovered consciousness and felt very well for two weeks. During that time he was allowed to be up in a wheel chair, but the edema returned. Two months after admission, the patient complained of urinary retention with pain in the lower abdomen, which was distended and rigid. Voluntary voiding followed the application of heat, but the patient's condition rapidly grew worse and he died twenty-four hours later.

At autopsy the entire gastroenteric tract was markedly dilated. The ileum, jejunum, cecum and the lower portion of the ascending colon had a purplish-black appearance, abruptly limited above and below. The stomach was enormously dilated, but the mucosa, save for being flattened, presented no abnormal changes. The duodenum was not remarkable. The wall of the gangrenous portion of the enteric tract was friable but no perforation was found. The mucosa of the uninvolved colon appeared normal. The walls of the mesenteric arteries were markedly thickened, and in the smaller branches small plugs of thrombi were found, but there was no evidence of embolism. The heart weighed 500 gm. The myocardium had a grayish-red, cooked appearance. The coronary arteries and the aorta were tortuous and revealed large atheromatous plaques in the intima. In the abdominal portion of the aorta early calcification and ulceration were found.

Microscopic examination of the ileum, jejunum and cecum revealed marked atherosclerosis, both of the large and of the small vessels supplying the enteric tract. The arterioles of the mucosa and submucosa were especially involved so that there was almost complete obliteration of their lumina. The areas supplied by these vessels were edematous and diffusely infiltrated with polymorphonuclear leukocytes. The mucosa was extensively necrotic, resulting in loss of all normal cellular outlines. Microscopic sections from other viscera presented marked arterioloatherosclerosis.

Pathologic diagnoses: diffuse arterio- and arteriolosclerosis, with massive gangrene, of the enteric tract; myocardial degeneration; generalized chronic passive congestion and toxic changes in the viscera; syphilitic aortitis; subacute bronchitis with moderate pulmonary edema.

Discussion. The outstanding characteristic which these cases had in common was sclerosis of the smaller vessels in the gastro-enteric tract, associated with localized areas of necrosis. There was also some degree of generalized arteriosclerosis.

Only one patient, N–30–304, presented symptoms which might be expected in connection with the gastro-enteric lesions found at autopsy.

A hypothesis suggested by the nature of these lesions is that

gradual occlusion of the vessels decreased the nutritional supply to such an extent that bacterial invasion became greatly facilitated, and there resulted extensive ulceration and gangrene of the mucosa and submucosa.

Summary. Three cases of extensive ulceration and gangrene of the gastroenteric tract are described in which these lesions are attributed to mesenteric arteriosclerosis.

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EMETIN AND THE TREATMENT OF AMEBIC COLITIS.*

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Emetin has become a popular drug in the treatment of intestinal protozoal infections and also in a number of other conditions, where the indications are much less definite. That its indiscriminate or unskillful use is dangerous, is well attested by reports of fatalities and by the frequent observation of serious poisoning symptoms. This was stressed by the writer as early as 1916.[1] Emetin poisoning shows itself clinically in three chief syndromes. These arise (1) in the gastrointestinal tract; (2) in the nervous system, and (3) in the circulatory system. Deaths have been reported from the effects under Group 3. In addition, there may be a severe local reaction to hypodermic injection, sloughing with intramuscular injection, and a definite cumulative action must invariably be remembered.

1. In the gastrointestinal tract, when taken by mouth, emetin is known to cause salivation, nausea and vomiting, all secondary to local irritation in the stomach. The effects of larger doses on the intestinal tract are not always remembered. In animals large doses hypodermically cause nausea, vomiting, purging with blood in the excreta, collapse and death in a period of hours. Excessive doses hypodermically or intravenously may result in death from collapse

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and heart failure with no vomiting. In animals, death within twenty-four hours may show little in the way of postmortem changes other than a general gastroenteritis. In dogs there is often intestinal ulceration. These things indicate strongly that emetin is excreted through the intestinal mucosa, thereby causing local irritation and ulceration.

In the human patient, diarrhea and dysentery *in sensu strictu*, are easily produced either by rapid overdosage or by cumulative action of too long continued dosage. It easily happens that the diarrhea due to amebic infection is continued as an emetin diarrhea. The indiscriminating observer is prone under these conditions to continue the emetin too long or even to increase the dosage. These possibilities attend the hypodermic use of emetin. By mouth the salts and various combinations of emetin are more apt to cause nausea and vomiting if released in the stomach, but may do so even in enteric-coated containers. This may be due to reverse peristalsis carrying the alkaloid forward into the stomach, to partial disintegration of the salol or keratin coating in the stomach, or to excretion of absorbed drug through the stomach mucosa. We need better information as to the nature of emetin loss from the body, the relative amounts and channels of excretion, the breakdown or detoxication of the drug in the body and the rate at which these processes occur.

2. In the nervous system, emetin also shows a powerful action which is undoubtedly operative some time before symptoms appear. We need here, too, more information as to histologic changes produced, selective action on different parts of the nervous system, and the factors that delay restoration to normal. Clinically, peripheral neuritis and edema are seen as evidence of emetin poisoning. The patient complains of swelling of the feet and ankles, often of a pretibial edema, attended by weakness, sometimes by dull or stabbing pains, and by paresthesias. At times the neuritic pains seem to localize in the joints, simulating an arthritis. This is also noted in relation to the peculiar arthritis often associated with bacillary dysentery. The hands and forearms are less frequently affected. Dyspnea on exertion, low blood pressure, and fast pulse are intimately related to the neuritic symptoms but whether they represent entirely a separate action on the heart, or involvement of the vagus and sympathetic nerve systems, or a composite action, including both peripheral nerves and heart, is at present unknown. In any case, emetin poisoning clinically often presents a picture of edema, peripheral neuritis, weak heart and low temperature and blood pressure, which is almost indistinguishable objectively from one type of beriberi. It raises a question worthy of study as to the influence of the vitamin B-1 (vitamin G) balance in the body on the development and character of symptoms of emetin poisoning.

3. In the circulatory system, emetin in toxic dosage seems to act

both on the controlling nerve mechanism and on the intrinsic musculature of the heart. Fast pulse and lowered blood pressure are clinical danger signs and should be detected and carefully regarded. Dyspnea on exertion and weakness are equally important. The lowered blood pressure may in itself partly or entirely determine the fast pulse rate, or may be a joint result of decreased peripheral vessel resistance with lowered dynamic power in the heart muscle. It is apparently connected closely with the peripheral neuritis and edema. J. H. Rinehart, in the Department of Pathology of the University of California Medical School, has observed necrosis of cardiac muscle fibers in cats receiving lethal and sublethal doses of emetin. Observations on the intrinsic and extrinsic nervous system of the heart are needed. Auricular fibrillation may be a direct result of emetin poisoning and may cause death. An example of the danger of disregarding the usual danger signals of emetin poisoning, as well as of exceeding a safe total dosage (*vide infra*), is furnished by the case reported by F. J. Leibly,[2] where neither blood pressure nor pulse rates are recorded except in the terminal hospital charts, and where nausea, vomiting and peripheral neuritis were not properly regarded. In this case, in addition, the actual total dosage of emetin exceeded safe limits (1.28 gm. or 21 grains by the author's record, which does not include additional emetin from four doses of ipecac totaling 9.2 gm.)

In general, the clinical similarity is striking between the heart of emetin poisoning and the beriberi heart. Rinehart's observation noted above, is at variance apparently with the statement in Cushny's Pharmacology (Edition IX, edited by Edmunds and Gunn) as follows, "Emetin injected into a vein weakens the heart's action, and induces a fall of blood pressure, but when it is injected subcutaneously or given by the mouth, the heart is not affected directly." Our own experience indicates a direct action of emetin on the heart, regardless of the method of administration. On theoretical grounds, and because of our respect for as yet unknown factors in the action of emetin, we have never used it intravenously.

During the past year extensive studies have been conducted in this Institute in collaboration with the Department of Pharmacology of the University of California Medical School. A long series of drugs is being investigated and some promising new additions to the therapy of amebiasis are being studied. Progress reports on these studies have appeared in special journals. Many older and less common drugs have also been studied. It is not our purpose here to discuss this work which doubtless will modify our therapeutic methods in the future. We wish to present here a plan of therapy for amebiasis which we find highly effective at present, and which can and must be modified to meet the conditions in each individual patient, or as better drugs may be found.

Modification and adaptation are necessary in the treatment of any

chronic disease, very especially in amebiasis. The desiderata are easily enumerated. Lacking a quick, powerful and safe specific, the physician seeks a form of treatment which will give a maximal percentage of cures, with the minimal risk to the patient and the least possible interruption of his daily activities. These points have been kept in mind constantly in the gradual development of the method here described.

The criterion of cure in amebiasis is difficult of establishment. We have somewhat arbitrarily set the definition of cure as an interval of three months after termination of treatment with no evidence of histolytica cysts in the stools on adequate examination. Amebiasis is not a self-limited disease and as a rule will persist until eradicated by drug therapy. The late Dr. W. E. Musgrave has described spontaneous cure as a rare occurrence and cure following an acute intercurrent disease. These points are worthy of careful study. Certainly their occurrence is unusual at least. Adequate examination means both direct and concentrated smear examinations by a really competent technician. Stool culture as a routine adds very little to the accuracy of diagnosis, and diagnosis, regardless of everything else, depends on one thing only, microscopic demonstration of Entamœba histolytica. Active amœbas are less characteristic and should not receive positive identification until after fixation and iron hematoxylin staining. The cysts are characteristic and are more valuable for direct diagnosis. Cysts rarely appear in a diarrheic or dysenteric stool. *Per contra*, active forms are much less common but may occasionally be seen in a formed or even in a constipated stool. By the inexperienced eye, active forms are easily confused with leukocytes, pus cells, macrophages and fixed tissue cells. While Charcot-Leyden crystals are usually found in the presence of cysts, these crystals alone are not pathognomonic of amebiasis. Their significance and method of formation are not known. They may indicate an allergic tissue reaction. It is interesting in this connection to recall the frequency of local mild allergic reactions at the site of emetin injections through the skin, as also the long-described ipecac hay fever, not infrequently set up by breathing in powdered ipecac root.

So far as we know, the only natural portal of entry of amebic infection into the human body is through the intestinal tract after ingestion of amebic cysts. Active forms of Entamœba histolytica never transmit the infection. The ingested cysts have been shown by Dobell to excyst in the lower small intestine, a single active amœba being gradually extruded through a pore in the cyst wall. Study of amebic invasion of the small intestine is greatly needed. If it occurs to any considerable extent, it might well be a precursor of sprue, or set up a specialized functional pathology associated with fatty diarrhea. The newborn active amœba by a peculiar process subdivides into 8 new amœbas which very soon penetrate

the mucosa of the large intestine, either through a crypt or by penetration between lining cells or by histolysis of the lining-cell layer.

In the submucosa minute abscesses are formed. These enlarge and burrow through to the lumen of the bowel, pointing as small yellow spots which rupture to form small ulcers. A number of these small abscesses or ulcers may coalesce and the result is a large ulcerated area with deeply undermined raised edges. The mucosa between ulcers is healthy. Active amœbas are found in the edges of healthy tissue, and cysts appear only in the lumen of the bowel.

The parasite-host balance must be understood. The optimum conditions for the parasite are absence of diarrhea, dysentery or other bowel symptoms. If diarrhea is present, active amœbas are carried away from the host's body and invariably perish. If no colonic symptoms are present, amœbas leave the body in the form of cysts, which alone can transfer the infection to a new host.

In long-standing chronic cases there is apt to develop a considerable amount of fibrous tissue mixed with leukocytic and inflammatory deposits. This type of reaction is probably due to secondary bacterial infection as amœbas alone cause very little tissue reaction. It is probable that the amebic infection is usually more or less complicated by bacterial infection. This does not seem to be a symbiosis, as Cleveland and Sanders[3] have finally succeeded in raising Entamœba histolytica in bacteria-free cultures by the use of cat liver *in vivo*. The bacterial infection is better considered as a complication which tends to increase the inflammatory reaction, produce more fibrous tissue, and normal tissue destruction, and set up a more or less independent type of lesion which has two important bearings on treatment. In the first place, the infiltration and thickening of the intestinal wall allows nests of amœbas to remain relatively inaccessible to drugs. In the second place, the pathologic picture remains more or less undisturbed by destruction of the amœbas and constitutes an entity in itself which has two types of symptoms. The first of these types is due to the fact that the infiltration and production of inflammatory and fibrous tissue leads to constrictions or stenoses, dilations and masses in the bowel wall. The second type of symptoms consists of the persistent colitis, diarrhea or dysentery, and constitutional effects resulting from active bacterial infection and interference with normal intestinal function. This is the explanation of cases difficult or impossible to cure after several thorough courses of treatment. Surgical measures may be necessary and the surgery of amebiasis requires separate consideration.

Treatment. The treatment of intestinal amebiasis must be carefully designed to meet the indications of biologic, pathologic, pharmacologic and clinical needs, which have been outlined. The major influence of the drugs used must evidently be exerted on amœbas lying deep in tissues and not on any contents of the bowel itself. In general an avoidance of bulk and roughage in the diet is

desirable, both to promote drug absorption and to relieve irritation of the intestine. It is questionable whether lowering starch intake has any special effect, as the active amœbas are feeding on tissue juices and not on starch grains in the intestinal contents.

Just as in malaria, duration of treatment is of extreme importance and the percentage of cures will rise in direct proportion to it up to a period of ten to twelve weeks. In other words, the total course of treatment should extend over ten to twelve weeks. It is worth repeating that the aim of this treatment is to give a maximal percentage of cures, with minimal risk to the individual patient and the least possible interruption of his ordinary activities. We will sketch here a fairly standard course, attempting to meet all the requirements, and urging again that it must be adapted individually to each patient, often with elective additions which will be noted later. The course is designed for ambulatory patients and no particular advantage has been noticed from keeping the patient in bed during part or all of it. Here again concomitant conditions, weak circulatory system or dysentery itself, may make bed rest necessary. The dosages advised are for adults of medium average weight (60 to 70 kilos) up to sixty or sixty-five year of age.

Drugs are initiated by a series of six daily hypodermic doses of emetin hydrochlorid of 1 grain (0.065 gm.) each. These are followed consecutively by six daily doses hypodermically of ½ grain (0.0309 gm.) emetin hydrochlorid, making a total of 9 grains of emetin. Clinical experience points definitely to a maximum safe dosage of 12 grains (0.80 gm.) in a single course. Anderson and Leake[4] in this institution have demonstrated experimentally that the dose of emetin should not exceed 10 mg. per kilo of body weight, if toxic symptoms are to be avoided. The patient is then given arsenic in the form of acetarsone ("Stovarsol"), 1 tablet (0.25 gm.) twice daily after food for ten days, a total of 20 tablets. This series is followed by seven to ten days of chiniofon ("Yatren"—German imported) given both by mouth and in rectal irrigations. The patient takes 1 chiniofon pill (0.25 gm.) after each meal for this period and on the evening of each day observes the following procedure. Two hours before bedtime, a cleansing enema of 2 per cent sodium bicarbonate (3 pints) is taken. At bedtime, in fact while lying on the left side in bed, 6 ounces of warm water containing a powder of 5 grams chiniofon is slowly instilled into the rectum by the patient himself, using a soft rubber ear syringe of 1- or 2-ounce size for the purpose. The patient must not assume a vertical posture after introducing the chiniofon solution. The solution is retained overnight, usually with no difficulty.

After the chiniofon course, we prefer to allow a week on an iron, strychnin and quinin tonic. This is followed by 1 grain pills of bismuthous emetin iodid with enteric coating, three each day to a total of 20. These can be given before or after meals, or altogether

at bedtime. If they excite gastric or intestinal irritation, the daily number should be reduced but the total kept constant. This course is followed by a second series of hypodermic injections of emetin hydrochlorid, $\frac{1}{3}$ or $\frac{1}{2}$ grain each daily, to a total of 6 treatments. This gives a maximum of 7 grains of emetin in the second series including the emetin iodid by mouth, which contains 20 per cent emetin.

In regard to acetarsone, we found that 3 tablets daily gave symptoms of arsenic poisoning in 1 patient in 6. Two per day rarely cause symptoms but if they appear, the drug is stopped at once and not repeated. The symptoms of poisoning are gastrointestinal irritation, lumbar pain, renal irritation, rashes especially involving palms and soles, joint pains and fever. Close watch is kept of the blood pressure, pulse rate and evidence of weakness or edema, throughout the treatment with reference to emetin poisoning. Should symptoms appear, treatment is interrupted for a few days or longer and continued with smaller dosage and rigid supervision. Sometimes with bed rest adequate treatment can be administered without toxic symptoms in such patients. In the hypodermic courses, no injections are given on Sundays. At the termination of the course, elixir of iron, quinin and strychnin is given by mouth for one month.

In addition to the course as outlined, two other adjuvant features must be available. Often the success of treatment depends on one or both of them. The first consists of the use of colon irrigations where constipation is in evidence or where colitis is fairly acute or ulceration extensive. These irrigations should be copious, with proper posture to secure spreading of the colonic mucosa by the fluid, and include saline and soda solutions, 1 to 5000 quinin hydrochlorid, 1 to 2500 emetin hydrochlorid and 1 to 5000 potassium permanganate. The second adjuvant treatment consists of the use of simple or reinforced autogenous total stool vaccines. These are of particular value where constitutional effects of amebiasis are in evidence, where the symptom course is chronic and where the pathology shows the influence of bacterial infection. Vaccine doses can be given hypodermically, with increasing size, at weekly intervals, during the general treatment as outlined.

Innumerable other drugs have been recommended and used in various parts of the world. Better drugs are now being sought in our laboratory. We not infrequently use one or more of these others in the course of treatment. However, on the whole, our best results have been along the lines indicated. Chaparro amargosa, Kurchi, auremetin, and antimony emetin iodid have been definitely abandoned.

It remains to say that in chronic cases complicated by much fibrous reactive tissue and bacterial infection, elimination of amœbas is by no means certain to cure the dysentery which may assume the

type of a typical chronic ulcerative colitis. In such cases our results have been best along the lines advocated by Bargen. Appendicostomy, with through and through irrigations over a period of time, followed by appendectomy, is another valuable recourse in some chronic patients. Amebic appendicitis and hepatitis cannot be discussed within the scope of this paper.

Conclusions. 1. Emetin is a powerful, dangerous and valuable remedy whose complete action is not yet known.

2. It must, therefore, be handled with caution and with constant watch for initial symptoms of emetin poisoning.

3. The treatment of intestinal amebiasis must cover a sufficient duration of time, irrespective of symptoms.

4. The course of treatment as outlined can be modified to the requirements of individual patients. The total amount of emetin given in 1 course must not exceed 0.010 gm. per kilo of body weight.

5. The ideal treatment must cure the maximal percentage of patients, with minimal risk, and with least possible interference with the patient's usual activities.

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THE ADVANTAGES FOR AN ATMOSPHERE CONTROL ROOM OF A QUASI-CONTINUOUS RECORD OF OXYGEN AND CARBON DIOXIDE.

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The oxygen concentration is the most vital of the variable atmospheric conditions requiring constant control for the safety and welfare of the patients in a clinical atmosphere control room. The carbon dioxide concentration is also an important variable, and

should be subjected to a rational and elastic control in accordance with the clinical needs of the patient. It can spontaneously increase to 10 or 100 times its value in the outer air, depending on the gas leakage from the room and on the method of decarbonation used. The two other important variables, namely, air temperature and relative humidity, are readily subjected to automatic and continuous measurement with a suitable recording instrument, which aids materially in their adequate control. A similar degree of control for the chemical composition of the air was unavailable, however, until the writers showed that it was possible to apply the thermoconductivity method of gas analysis* to the measurement of oxygen and carbon dioxide in air mixtures of varying oxygen concentration.

The chemical composition of the air in an oxygen chamber is obviously determined by the rate of oxygen delivery, the rate of metabolic exchange in the room and the rate of gas leakage into and out of the room, further modified by sudden changes due to the opening of doors and cabinets. A disturbance in the balance between these factors can cause the composition to vary from one very rich in oxygen to one as poor in oxygen as ordinary air, or even poorer, and marked departures from the desired concentration may persist undetected for hours if occasional chemical analyses are relied upon as the sole aid to control. These undetected variations assume an especially grave significance in the treatment of pneumonia and of heart disease, where an increased oxygen supply is needed to raise the low percentage saturation of the blood hemoglobin. In cases involving extreme anoxemia, the term oxygen deprivation becomes highly relative, and in some cases may apply when the atmosphere contains as much as 25 or even 35% oxygen. An oxygen deprivation permitting 15% unsaturation of the blood for even one or two hours will greatly increase the hazard to the patient. Moreover, excessively high oxygen concentrations (70% and over) appear to have an irritant and toxic effect when continuously administered, and are therefore to be avoided.†

For the safety of the patient, therefore, as well as for any systematic approach to the study of oxygen therapy, it is essential to employ some continuous or quasi-continuous method of gas analysis. The thermoconductivity instrument with which we have been experimenting for the past six months records on a single timed chart at intervals of one minute both the per cent concentration of oxygen and the per mille concentration of carbon dioxide. Similar, complete records could not be obtained by direct chemical

* A Thermal Conductivity Recorder for Oxygen and Carbon Dioxide for Clinical Atmosphere Control. Grace Lubin, Ph.D., and Jesse G. M. Bullowa, M.D. Proceedings of the Society for Experimental Biology and Medicine, 1930, **27**, 568. See also Industrial Analysis and Recording of Carbon Dioxide and Oxygen in Air, William F. Hamilton, Industrial and Engineering Chemistry—Analytical Edition, 1930, **2**, 233.

† The Pathological Effects of Atmospheres Rich in Oxygen. H. T. Karsner, J. Exp. Med., 1916, **23**, 149.

analysis in the hands of two skilled technicians, with their reliefs, working continuously day and night.

Description of the Apparatus. The principle upon which our instrument depends is that heat is conducted away from a hot wire more rapidly by some gases than by others. Changes in the composition of a gas mixture surrounding an electrically heated wire thus affect the equilibrium temperature of the wire, causing variations in its electrical resistance which can be measured with a sensitive galvanometer. The resistance is not measured directly, but is compared by means of a Wheatstone bridge arrangement with that of an identical wire in a separate compartment of the cell, filled with a reference gas.

Oxygen is measured in a single-flow cell, a dried and decarbonated sample of the unknown air mixture being compared with a sample of ordinary dried air of fixed composition. Carbon dioxide is measured in a separate double-flow cell, to counteract the effect of a fluctuating oxygen concentration,* the two compartments containing respectively a dried sample of the air mixture and a dried and decarbonated sample of the same mixture. In our installation the sampling is carried out continuously, air being pumped from and returned to the oxygen chamber. The structure of the cells is such as to offset the effect of changes in rates of gas flow. Variations in room temperature have no effect on the carbon dioxide cell, and the oxygen cell is protected by an air thermostat.

A single recording galvanometer is used, the terminals of which remain in contact with each cell for thirty seconds. Just before the contact is shifted, the pointer is depressed against a double-colored inked tape, making a mark on a timed chart moved by clockwork. Two curves are thus obtained, each having its individual color and being made up of observations at intervals of one minute. The time lag for the thermal cells used by the writers is seven minutes, which is no greater than that necessary for accurate chemical analysis. The scale readings represent roughly per cent of oxygen in the dry decarbonated mixture, and per mille of carbon dioxide in the dry air mixture. For greater accuracy the scale readings are corrected by an empirical calibration curve, giving oxygen concentration to within $\pm 1\%$, and carbon dioxide to within 0.1%. The instrument was made by Charles Engelhard, Inc., of Newark, N. J. It is shown in Fig. 1, as installed on the outer wall of the oxygen chamber. The carbon dioxide curve (left) and the oxygen curve (right) can be seen on a twelve-hour section of the chart. A section of chart is also shown in Fig. 2.

* In commercial practice, where thermoconductivity instruments have been used for several years for carbon dioxide measurements, the disturbing influence of oxygen is negligible, since the oxygen concentration is almost constant in the flue gases usually measured. Moreover, the instruments are much less sensitive to changes in oxygen than to changes in carbon dioxide concentration. They are affected by the two gases in reverse directions.

Supervision Required. The dehydrating and decarbonating train require changing about twice a week, the clockwork must be wound once a week and the chart renewed once a month. The 12-volt storage battery which supplies current to the cells requires the usual supervision, and the current must be maintained strictly constant, either by the alternate use of two batteries, or with the use of a suitable trickle charger. It is well to check the recorder from time to time by chemical analysis of the air in the oxygen room. It can also be checked by drawing ordinary room air through

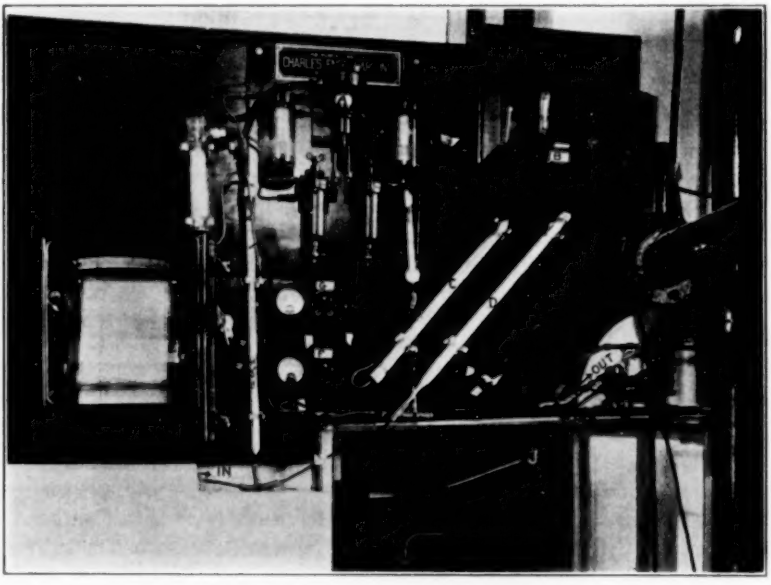

FIG. 1.—Oxygen and carbon dioxide recorder for atmosphere control room at Harlem Hospital. *A*, double-flow CO_2 cell; *B*, single-flow O_2 cell in air thermostat; *C*, drying tube; *D*, decarbonating tube; *E*, recording galvanometer, showing 1.9% CO_2 and 43% O_2; *F*, milliamperemeter and rheostat for CO_2 cell; *G*, milliamperemeter and rheostat for O_2 cell; *H*, inlet to rotary pump (on the floor); *I*, outlet from rotary pump; *J*, thermohydrograph in oxygen room; *IN*, sample intake from oxygen room; *OUT*, sample outlet, return to oxygen room.

the cells, in which case the oxygen concentration should be between 20 and 21%, and the carbon dioxide between 0 and 1 per mille. Pure, dry oxygen should register 100% on the oxygen curve.

Leaks in the adsorption train are especially to be avoided, and to this end it is well to use brass connections wherever possible and to protect the joints with paint.

Practical Applications. The clinician will readily appreciate the value of a complete record of the per cent oxygen and carbon dioxide to which his patient has been subjected. A twenty-four-hour

section of the chart can be read at a glance and provides an irrefutable check on the operating conditions and full and accessible data for studying and controlling the administration of oxygen and the therapeutic value of one or two or even greater per cent of carbon

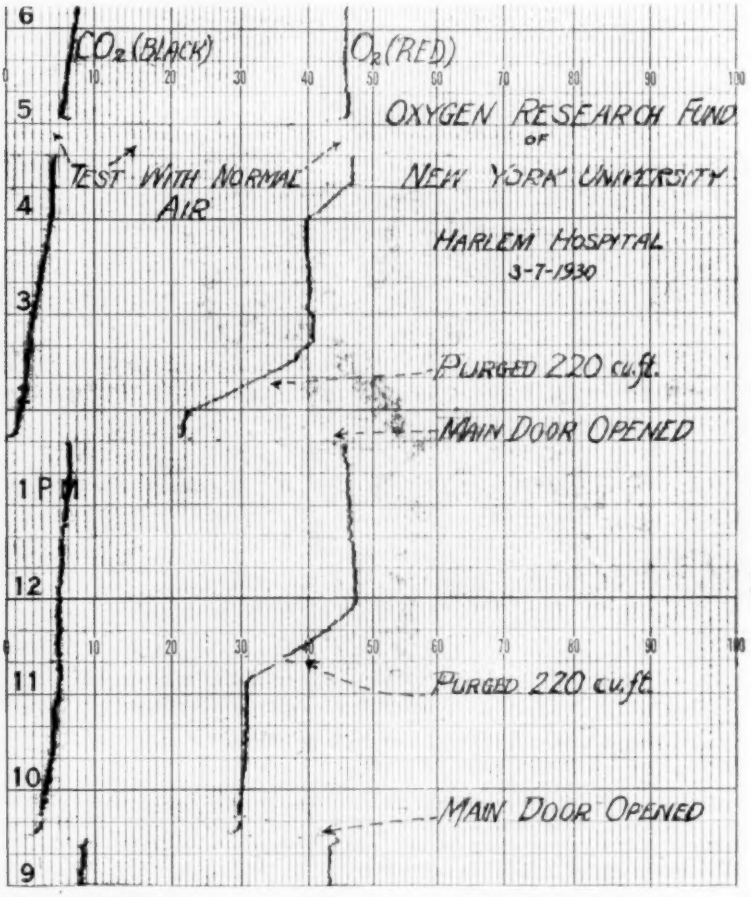

FIG. 2.—Reproduction of record showing per cent concentration of oxygen and per mille concentration of CO_2, as indicated by the figures across the scale. The right curve is oxygen, the left CO_2. On the original chart the O_2 appeared in red and the CO_2 in black. Both the lines are dotted, and are made on the moving chart by pressure of the galvanometer needle against a typewriter ribbon. Records are made for O_2 and CO_2 alternately on the half minute so that the vertical distance between the dots on any curve represents the lapse of a minute in time.

dioxide. We have found, furthermore, that the record promotes efficiency and economy in the operation of atmosphere control chambers.

The slope of the oxygen curve is a guide as to the correct rate of

oxygen delivery, and, by aiding in the prompt detection of leaks from the chamber, reduces the required rate of delivery to a minimum. After the chamber has been purged, that is, rapidly filled, to the desired oxygen concentration, the oxygen curve will be a vertical line only if delivery exactly balances consumption. A slight slope in the curve indicates that the oxygen is being supplied too quickly or too slowly. This feature is important since delivery rate cannot be estimated in advance from the metabolic needs of the patient or patients, which are invariably small (less than a liter per patient per minute), compared to the loss from constant leakage and from opening doors and cabinets.

Gas leakage from oxygen chambers must obviously vary widely with their construction and size, and the details of their special equipment. To quote two specific examples, in one oxygen chamber of 2000 cubic feet capacity, and not equipped with a gas recorder, a delivery rate of 15 liters per minute and daily purging with about 400 cubic feet of oxygen are required for a single patient, when the desired oxygen concentration is 50%. Obviously, the oxygen concentration in this chamber has fallen considerably below the desired level before the daily purging. At the time the gas recorder was installed in our own chamber, which has a capacity of 1000 cubic feet, a rate of 15 liters per minute and daily purgings were also required, due largely to the faulty design of a new dehydrating unit. As a result of the constant reminder of oxygen wastage provided by the sloping line on the recorder chart, the design of the dehydrator was changed, yielding a definite reversal in the slope of the oxygen curve. A vertical line was then obtained at 50% concentration when the rate of flow was reduced to 9 or 9½ liters per minute, with 2 adult patients, 1 child and a nurse constantly in the chamber. Purging then became unnecessary excepting to replace the oxygen lost in admitting or releasing patients. The saving in oxygen in twenty-four hours amounted to about 300 cubic feet for reduced rate of flow and at least 300 cubic feet for the elimination of purging. Assuming the very low price of $1 per 100 cubic feet, this saving would in four or five months more than offset the cost of installing an automatic recorder.

In addition to the more or less permanent leaks from an oxygen chamber, temporary leaks occur from time to time, due to aging of rubber gaskets and paint seals, and occasionally to the carelessness of the chamber attendants, who may fail to lock a door tightly, or may neglect to replace a plug in the taps provided for wet and dry bulb measurements in the ducts. These leaks, which would ordinarily remain unnoticed for hours or days, become at once apparent on the recorder chart, and can be promptly localized and corrected.

The detection of leaks is of great importance not only in maintaining the required oxygen concentration, but also in preventing

unexpected additions of unconditioned air, which may greatly increase the load upon the dehydrating unit. The importance of this factor is very evident in the Atlantic seaboard regions, especially during the hot and humid summer months. In our chamber at the Harlem Hospital, the relative humidity is maintained at 30 to 45%. During the winter months the conditioned air must be only slightly drier than the outer air, the difference being on the average about 3 or 4 grains per pound of dry air. About 9 or 10 pounds of moisture are removed from the chamber by the dehydrator in twenty-four hours. During the summer months this difference in absolute humidity rises to 20 or 30 grains per pound of dry air. As a result, the amount of moisture to be removed from the chamber increases in the summer by at least 50%, and may be more than doubled when precautions are not taken to minimize air leakage.

The recording instrument has been of further use in curtailing oxygen losses involved in the necessary manipulation of the doors and cabinets. By observing the drop in oxygen concentration on the chart, the nurses supervising a change of patients in the chamber have so improved their method as to reduce the loss due to the withdrawal of one patient and substitution of another from about 10% or 100 cubic feet to about 4% or about 40 cubic feet. This represents a saving of 60 cents, assuming the low rate for oxygen mentioned above. The record is a mute and irrefutable account of what has transpired, and a check on and a stimulus to the personnel.

The carbon dioxide curve has also been of advantage in enabling us to study the relative efficiency of various decarbonating methods. The results of these studies, which will be presented in detail elsewhere, suggest that in most tents and chambers the chemical methods employed remove a relatively small proportion of the carbon dioxide that is developed, most of the carbon dioxide being blown out through the prevailing leaks.

Summary. (1) By means of a thermoconductivity analyser, it is possible to make quasi-continuous record of the per cent of oxygen and carbon dioxide in an atmosphere control room. (2) We have found that the record thus provided has contributed to the scientific observation of patients subjected to controlled atmospheric conditions, and to the efficiency and economy with which these conditions can be maintained.

REVIEWS.

A Manual of the Common Contagious Diseases. By Philip Moen Stimson, A.B., M.D., Associate in Pediatrics, Cornell University Medical College. Pp. 351; 40 illustrations and 2 plates. Philadelphia: Lea & Febiger, 1931. Price, $3.75.

A practical, well-written handy little volume that reflects the author's clinical and teaching experience. It includes chapters on the principles of contagion, serum reactions, diphtheria, Vincent's angina, scarlet fever, measles, rubella, whooping cough, mumps, chickenpox, vaccination against smallpox, epidemic meningitis and poliomyelitis. There is an excellent concluding chapter on the general management of contagious diseases, with detailed description of the technique for dealing with these conditions in hospitals, schools and in the home. The author's hope that practitioners and students will find this book "a convenient and serviceable friend" is more than justified. R. K.

Recent Advances in Chemotherapy. By G. M. Findlay, O.B.E., M.D., D.Sc., with a Foreword by C. M. Wenyon, C.M.G., C.B.E., M.B., B.S., B.Sc., F.R.S. Pp. 532; 15 illustrations. Philadelphia: P. Blakiston's Son & Co., Inc., 1930. Price, $3.50.

This is an unusual little book containing a large amount of valuable material particularly from chemical sources which is difficult to obtain from general reading. The earlier chapters deal with the chemotherapy of helminthic infections, amebiasis, malaria and leishmaniasis, trypanosomiasis and piroplasmosis. There are valuable summaries from the literature of the use of carbon tetrachlorid, thymol, betanaphthol, santonin, and emetin. Drugs such as kurchi, little known in American practice but evidently highly regarded in tropical countries, are also discussed. Many important details concerning plasmochin are given and the discussion of antimony therapy in various conditions is the most complete the Reviewer has seen in English. This may also be said of the discussion of the treatment of trypanosomiasis which contains a description of the much discussed and chemotherapeutically significant Bayer 205,

heretofore obtained with difficulty from the literature. The section on tryparsamid would bear fuller treatment, particularly with reference to its use in neurosyphilis. The classification adopted in the book, however, is such that the consideration of this drug appears in two different portions of the text. Apparently it has not been the author's intention to cover the detail of the chemotherapy of syphilis and this gives this portion of his material a somewhat sketchy quality. None the less, there is again a great deal of information especially on bismuth preparations which would escape the ordinary reader. The sections on the therapy of leprosy are excellent and reveal very clearly the advance which has been made in the treatment of this disease not only with the ethyl esters of chaulmoogra oil but with sodium salts such as alepol. The gold therapy of tuberculosis is briefly but interestingly discussed. Each chapter contains an excellent bibliography though one notices the absence of titles which one might expect to appear in a survey of this sort. Such criticism, however, is trivial in comparison with the merits of the work which is a valuable source-book for those concerned with its field, to say nothing of the broadly read medical man.

J. S.

DOSAGE TABLES FOR ROENTGEN THERAPY. By PROFESSOR FRIEDRICH VOLTZ. Translated from the Second German Edition. Pp. 120; 21 illustrations. New York: Oxford University Press, 1930. Price, $2.50.

THIS book is an excellent one, describing the general rules for applying dosage in Roentgen ray therapy. It discusses the three basic physical factors; namely, spreading, absorption, and scattering, and illustrates these factors by excellent figures.

In practical Roentgen ray therapy the author considers seven special concepts: (1) The physical dose; (2) the biological dose; (3) the dosage quotient; (4) a percentage deep dose; (5) the effective dose; (6) the practical dose; (7) the absolute unit of dosage. All of these concepts are analyzed, described and illustrated beautifully. The data have been collected from a number of authorities and have been arranged conveniently so that they may be of practical assistance to everyone knowing Roentgen therapy.

Following this the author analyzes the methods of measuring. In Chapter V there are detailed tables of dosages giving factors that will assist one in quickly obtaining the dosage, both on the surface and at a depth. It is also possible with the factors given in these tables to determine the amount of surface irradiated, and to obtain the coefficient of absorption of the tissues.

This small book is extremely practical and will be a great aid to everyone doing Roentgen therapy. It does not require a profound

knowledge of physics to understand the factors given, or the laws that are analyzed. The text is very easy to comprehend, and is given in a precise form. H. P.

PRACTICAL MIDWIFERY FOR NURSES. By BETHEL SOLOMONS, M.D., F.R.C.P.I., M.R.I.A. Pp. 354; 136 illustrations. New York: Oxford University Press, 1930. Price, $2.75.

SIMPLY written and concise, containing everything of practical value to the maternity nurse this book should be invaluable to midwives. A logical arrangement of material carries the student from the basic anatomy and physiology of the reproductive organs to pregnancy, antenatal care and labor. Over 100 pages are devoted to abnormal conditions of pregnancy and labor and puerperium, in which more than half of the illustrations are included, with graphic descriptions of proper procedures during emergencies.

Of the three appendices to the book; the first contains prescriptions for liquid nourishment and some simple home remedies, the second a few definitions of abnormal conditions not previously mentioned; the third rules and regulations for English midwives. A glossary and index complete this well-planned and useful book.

M. S.

AN INTRODUCTION TO MALARIOLOGY. By MARK F. BOYD. Pp. 437; 82 illustrations. Cambridge, Mass., Harvard University Press, 1930. Price, $5.00.

THE book consists of a short foreword by the author, six chapters and a very complete index. Chapter I is devoted to brief discussions of the ancient and modern history of malaria, its introduction, spread and present status in North America, and its general geographic distribution. A full discussion of factors important in the natural history of malaria is presented in Chapter II. Malarial surveys are discussed and analyzed in Chapter III. Chapter IV deals with the natural history of Anopheline mosquitoes. Purposes, methods and application of Anopheline surveys are considered in Chapter V. A short section, Chapter VI, on the relation of surveys to control work, completes the text. Each chapter is amply supported by original references. Numerous well chosen illustrations and aids to the analysis of data supplement the text. Emphasis is properly placed on practical application. The book should be welcomed by students of tropical medicine, and health officials confronted with malaria control will find in it aid to the solution of many problems. H. R.

A Text-book of Gynecology. By Arthur Hale Curtis, M.D. Pp. 380, 222 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, $5.00.

This text is a clear and concise exposition of the fundamental principles of gynecology. Realizing the importance of a clear understanding of the pelvic infections in relation to other pelvic conditions the author discusses first the gonococcal lesions, the streptococcal, puerperal and postabortal, infections of the cellular structures of the pelvis and pelvic tuberculosis.

In the chapter on myoma uteri the author remarks on the constantly narrowing field for the use of radium therapy; he lays stress on the combined use of surgical diathermy and radium in the treatment of cervical carcinoma. Endometriosis is the subject of an excellent recapitulation of the present knowledge of the subject.

A rather unusual but timely chapter for a text-book on gynecology is the one on the management of the early months of pregnancy and their complications. Internal secretions are presented in a modern light, and quite sanely. The operative technique recommended conforms to standard practice although some exception might be taken to the perineal plastic operations suggested.

A note of conservatism, sometimes skepticism, runs through the book flavoring the personal opinions of an author who does not regard everything printed as proved. A short reference bibliography follows each chapter. The illustrations by Tom Jones beautifully correlate the text, there are also many very well chosen photomicrographs.

The style and form of the book are pleasing and it may be warmly recommended. P. W.

Physics of Radiology. By J. L. Weatherwax, M.A., Physicist, Philadelphia General Hospital. With a Foreword by Henry K. Pancoast, M.D., Professor of Roentgenology, University of Pennsylvania. Pp. 240; 136 illustrations. New York: Paul B. Hoeber, Inc., 1931. Price, $5.00.

A long-standing reproach applicable to not a few centers of radiologic therapy and medical investigation has been that the underlying physical principles were not sufficiently or properly utilized. The persistence of the unscientific "erythema dose" as the biologic unit of radiation will serve as an example. It is therefore both a hopeful sign and a valuable occurrence when a physicist with the general background and the applied experience of the author of this book sets out authoritatively yet practically the physical principles whose mastery are necessary for the scientific practice of radiology. E. K.

DIETETICS AND NUTRITION. By MAUDE A. PERRY, B.S. Pp. 332. St. Louis: The C. V. Mosby Company, 1930. Price, $2.50.

THE author endeavors to present in simple language the subject of dietetics in health and disease to meet the needs of training schools for nurses, physicians, teachers and others interested in this subject. There are discussed food requirements, including vitamins, mineral salts, together with a discussion of protein, fat and carbohydrate metabolism. Although the book is wide in its scope, its arrangement (sequence) is not as good as might be; definitions often leave much to be desired, as for example, "In nephrosis we may have edema, but uric acid and urea characteristic in many cases of nephritis are not found in the blood." L. J.

THE TREATMENT OF CHILDREN'S DISEASES. By PROF. DR. F. LUST, Authorized Translation of the 6th German edition with additions by SANDOR A. LEVINSOHN, M.D. Pp. 513. Philadelphia: J. B. Lippincott Company, 1930. Price, $8.00.

WHILE devoting itself largely to therapeutics, this book lays as much stress upon diagnosis as is necessary to give a concise clinical picture of the particular disorder for which treatment is advised. In this respect it will serve as an outline of the whole field of pediatrics. With this background, treatment is considered fully and explicitly, and in most conditions alternative forms of treatment are given.

The first part of the book considers therapeutics by subject. Nutrition, neonatal diseases, metabolic and constitutional diseases, diseases of the blood, endocrine disorders are considered in order. Following this diseases are considered by systems, then a section on infectious diseases, which is very complete. A chapter is devoted to skin diseases and finally a very good chapter on therapeutic technique.

The second part considers therapeutic agents in alphabetical order. A large number of these are included, many of which are foreign. It is very convenient to have in one place accurate information about many of these remedies. Dosage is carefully stated and discussed, the maximum and minimum dose for the infant, the preschool child and the school child being tabulated in almost every instance. In the dosage tables, allowance is made for the variations in the size of drops, and many incompatibilities and cautions are mentioned.

The book abounds in diet lists, calorie tables, infant feeding formulas and helpful suggestions. Numerous translators' notes are appended, most of which explain differences in American and

German usage. The Reviewer finds this a most estimable work, one of the handiest books he has ever seen, and without hesitation, can give it his full recommendation. J. S.

THE AFRICAN REPUBLIC OF LIBERIA AND THE BELGIAN CONGO, VOLS. I and II. Edited by RICHARD P. STRONG, Department of Tropical Medicine, Harvard University Medical School. Pp. 1064; 468 illustrations and 28 text figures. Cambridge, Massachusetts: Harvard University Press, 1930.

ACCUSTOMED as we are to the characteristically sumptuous publications of the Harvard Department of Tropical Medicine this most recent one on Liberia surpasses expectations. A complete biological survey of a little known region, it fascinates with its romantic humanism as well as instructing with its objective scientific studies. Only those who mistake seriousness for efficiency and dryness for scientific presentation will tend to scoff at the picture-book, story-book features of this report; but let us hope that they will be few compared to those who recognize its real and great importance for the many branches of the natural sciences with which it treats.

Volume I devotes almost half its space to an ethological survey and over 300 pages to human, comparative and plant pathology—descriptive and investigative. In the equally large second volume are found chapters on mammals, birds, reptiles and an especially complete one on insects. The 500 illustrations, well chosen and well executed, demonstrate how well many phases of widely differing stories can best be depicted in the graphic manner.

E. K.

A SYSTEM OF CLINICAL MEDICINE. By THOMAS DIXON SAVILL, M.D., London. Pp. 1019, 167 illustrations. Eighth Edition. New York: William Wood & Co., 1930. Price, $10.00.

THE present edition continues the same arrangement as was followed in the previous seven editions. There are inherently certain virtues and certain faults to such an arrangement. For those unfamiliar with the work it may be said that to the American reader it suggests a hybrid between a textbook of medicine and one on diagnosis without achieving the completeness of either. On the other hand, there is in it perhaps more detail than would be found in a one volume work of either of these types. O. P.

MICROBIOLOGY AND ELEMENTARY PATHOLOGY. By CHARLES G. SINCLAIR, B.S., M.D. Pp. 362; 102 illustrations. Philadelphia: F. A. Davis Company, 1931. Price, $2.50.

THIS new nurses' text, designed to satisfy the classroom and laboratory requirements of the courses in Microbiology and Pathology as prescribed by the League of Nursing Education, is done in a clear and pleasing style. The greater part of the work is given to a limited, but representative consideration of microbiology, and includes an historical outline, the characteristics, distribution and activities of microörganisms in general, and sufficiently detailed consideration of important groups, with examples of each. In discussing various organisms the pathologic lesions produced by them are presented. General pathology and so-called Clinical Pathology are treated very briefly. The paragraphs at the end of numerous chapters summing up the importance of various points to the physician as well as nurse are valuable. Especial reference is made to the terse definitions given new terms as they are introduced, and the skillful manner in which these definitions are unoffendingly repeated when the new term is used for the second time. The subject matter is accompanied by numerous illustrations, some of which are after standard texts, but many entirely new. G. K.

BOOKS RECEIVED.

NEW BOOKS.

Diseases of Children. By BRUCE WILLIAMSON, M.D. (EDIN.), M.R.C.P. (LOND.), Physician to the Royal Northern Hospital, London. Pp. 290; 50 illustrations. New York: William Wood & Co., 1931. Price, $3.50.

The Papyrus Ebers. Translated from the German version by CYRIL P. BRYAN, M.B., B.Ch., B.A.O., Demonstrator in Anatomy, University College, London; with an Introduction by PROF. G. ELLIOT SMITH, M.D., D.Sc., LITT.D., F.R.C.P., F.R.S., Professor of Anatomy, University College, London. Pp. 167; illustrated. London: Geoffrey Bles, 1930. Price, 10s. 6d.

Medical Clinics of North America, Vol. 14, No. 4 (Philadelphia Number, January, 1931). Pp. 240; 47 illustrations. Philadelphia: W. B. Saunders Company, 1931.

A History of Science. By WILLIAM CECIL DAMPIER DAMPIER-WHETMAN, M.A., F.R.S., Fellow and sometime Senior Tutor of Trinity College, Cambridge; Fellow of Winchester College. Pp. 514; 14 illustrations. New York: The Macmillan Company, 1931. Price, $4.00.

Chininum. By DR. MED. FRITZ JOHANNESSOHN. Pp. 232. Amsterdam: Bureau Tot Bevordering Van Het Kinine-Gebruik, 1930.

Annals of the Pickett-Thomson Research Laboratory, Vol. VI: The Pathogenic Streptococci, Monograph XI: The Rôle of the Streptococci in Scarlet Fever. By DAVID THOMSON, O.B.E., M.B., CH.B. (EDIN.), D.P.H. (CAMB.), Hon. Director, Pickett-Thomson Research Laboratory, St. Paul's Hospital, London; and ROBERT THOMSON, M.B., CH.B. (EDIN.), Pathologist to the Pickett-Thomson Research Laboratory. Pp. 470; illustrated. Baltimore: The Williams & Wilkins Company, 1930.

Calcium Metabolism and Calcium Therapy. By ABRAHAM CANTAROW, M.D., Assistant Demonstrator of Medicine, Jefferson Medical College, Philadelphia; with a Foreword by HOBART AMORY HARE, B.Sc., M.D., LL.D., Professor of Therapeutics, Materia Medica and Diagnosis, Jefferson Medical College, Philadelphia. Pp. 215. Philadelphia: Lea & Febiger, 1931.

The Development of Physiological Chemistry in the United States. By RUSSELL H. CHITTENDEN, Professor of Physiological Chemistry in the Sheffield Scientific School of Yale University, 1882–1922. Pp. 427. New York: The Chemical Catalog Company, Inc., 1930. Price, $4.50.

Sir D'Arcy Power: Selected Writings, 1877–1930. Anonymous. Pp. 368; illustrated. Oxford: Clarendon Press, 1931. Price, 25s., net.

Hieronymus Fracastorius: History of Medicine, Series No. 2 of the New York Academy of Medicine. Translation and Notes by WILMER CAVE WRIGHT, PH.D., Professor of Greek in Bryn Mawr College. Pp. 356. New York: G. P. Putnam's Sons, 1930.

Clio Medica, Vol. V: Physiology. By JOHN F. FULTON, M.D., Sterling Professor of Physiology, Yale University. Pp. 141; illustrated. New York, Paul B. Hoeber, Inc., 1931. Price, $1.50.

Das Wunder in der Heilkunde. By ERWIN LIEK-DANZIG. Pp. 208. Munchen: J. F. Lehmanns Verlag, 1930. Price, M. 3.60.

Ninth Scientific Report on the Investigations of the Imperial Cancer Research Fund. Pp. 156; illustrated. London: Taylor & Francis, 1930.

The sixteen articles in this report, covering a period of seven years, continue the reputation that this Institute possesses of being perhaps the leading one of its kind. The usual topics of modern cancer research are well represented. In many of the illustrations a practical stereoscopic effect is ingeniously obtained by "pseudoscopy." One wonders if in Fig. 6 of Plate XIV*a*, one is expected to practice pseudoscopy on the "elcsum" of the legend as well.

Cancer. By WILLY MEYER, M.D., Emeritus Professor of Surgery, New York Postgraduate Medical School. Pp. 427; illustrated. New York: Paul B. Hoeber, Inc., 1931. Price, $7.50.

Bioassays: A Handbook of Quantitative Pharmacology. By JAMES C. MUNCH, Director of Pharmacological Research, Sharp and Dohme; Pharmacologist, Bureau of Biological Survey, United States Department of Agriculture. Pp. 958; 22 illustrations. Baltimore: The Williams & Wilkins Company, 1931. Price, $10.00.

NEW EDITIONS.

Medical Biometry and Statistics. By RAYMOND PEARL, Professor of Biology in the School of Hygiene and Public Health, and in the Medical School, The Johns Hopkins University. Pp. 459; 89 illustrations. Second edition, revised. Philadelphia: W. B. Saunders Company, 1930. Price, $5.50.

With the ever increasing necessity for quantitation in the medical sciences such a book as this, by an acknowledged master of biometry, and written specially for the medical readers, can hardly have its importance emphasized. Following pleasant introductory defining and historical chapters, the author takes up in seventeen chapters and five appendices such topics as graphic representation, life tables, the probable error measurements of variation and correlation and curve fitting.

Practical Bacteriology. By T. J. MACKIE, M.D., D.P.H., Professor of Bacteriology, University of Edinburgh; and J. E. MCCARTNEY, M.D., D.Sc., Director of Research and Pathological Services, late Metropolitan Asylums Board, London. Third edition. Pp. 421. New York: William Wood & Co., 1931. Price, $3.50.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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The Pathogenesis of the Forms of Jaundice.—In the last few years important advances have been made in the knowledge concerning bile-pigment formation and excretion. There has never been much difficulty concerning the authenticity of the generally accepted concepts concerning the pathogenesis of the so-called obstructive type of jaundice, but there have been many and fantastic theories advanced in order to explain the mechanism of production of jaundice without obstruction. RICH (*Bull. Johns Hopkins Hosp.*, 1930, **47**, 338) writes that irrespective of the way the bile pigment is made, it is necessary that the liver get rid of it if jaundice is to be prevented and that in the so-called non-obstructive or hemolytic jaundice the condition of the excretory function of the liver must be considered. The paper is presented in order to set forth the studies that he and his associates have made in the rôle of the liver in jaundice in order to present certain principles which are of importance in the understanding of this morbid state and to present a classification of the forms of jaundice. Bile pigment (bilirubin) is made outside of the epithelial liver cells, carried to them by way of the blood and excreted in the bile passages. The bilirubin as it passes through the liver capillaries is selectively taken out from the blood by the hepatic cells and is excreted somewhat as a threshold substance. If jaundice has occurred it is necessary (1) for the threshold of the liver for bilirubin excretion to become greatly raised. This is purely hypothetical. (2) It would be necessary for bilirubin to be produced faster than the normal liver cells could excrete it. This may in theory happen, but is actually unlikely to occur because of the extremely high factor of safety for the liver. (3) The excretory mechanism of the liver must be so obstructed that the amount of bilirubin cannot be satisfactorily removed from the blood and, finally, (4) combinations of the above conditions. The third possibility does not occur as a purely functional depression of the excretory power of the liver, that is, without actual loss of cells through necrosis. There is no condition known at present which so represses the excretory function of the living liver cells that jaundice will occur because the normal quantity of bilirubin cannot be gotten rid of. The fourth possibility is the common one—increased

production of bile pigment associated with conditions which depress liver function. In conjunction with an attempted endeavor to classify jaundice on the basis of pathogenesis, the van den Bergh is of considerable importance, bearing in mind that bilirubin that has passed through the liver gives a direct reaction, whereas that which has not been acted upon by the liver cells gives the indirect van den Bergh. Rich presents a classification of jaundice based upon the idea that while it is possible to have hemolytic jaundice, such a term is an improper one, as the jaundice will not occur unless there is subnormal liver function. It is for this reason that he prefers to employ the term "retention jaundice" in contraindication to the other great type familiarly known as obstructive jaundice and which he chooses to call "regurgitative jaundice." In retention jaundice there is excessive urobilin in the stools and in the urine and indirect van den Bergh. Overproduction of bilirubin and the subnormal liver function in this type of jaundice may be produced by (*a*) anoxemia, which in turn may depend upon anemia (pernicious anemia, hemolytic jaundice, sickle-cell anemia, paroxysmal hemoglobinuria, mismatched transfusion or phenylhydrazine poisoning) or chronic passive congestion (cardiac decompensation); (*b*) febrile disease associated with anoxemia resulting from anemia and pulmonary consolidation; (*c*) immaturity of liver cells in the newborn (icterus neonatorum); (*d*) undetermined (Hanot's cirrhosis). Particularly to be stressed in the production of retention jaundice is anoxemia. Local anoxemia is responsible for necrosis of the liver cells, notably the cells about the efferent vein, which are particularly sensitive to the effects of a deficient oxygen supply, which results in the formation of atrophied cells which are unable to function as efficiently as normal ones. Consequently the bilirubin is not excreted in quantities comparable to that which the normal liver could excrete. In the second named type of jaundice, regurgitation jaundice, there occurs (1) either a rupture of the canaliculi caused by necrosis of the liver cells such as happens in chloroform or arsphenamin poisoning, yellow fever and acute yellow atrophy, or (2) obstruction of the bile ducts from plugging, stricture or pressure, as from gall stones, syphilitic cirrhosis or pressure of a tumor mass, or (3) a last-named group, classed as undetermined, seen in catarrhal jaundice. In this article Rich discusses quite fully the various forms of jaundice and offers a classification, which has been succinctly abstracted in the above paragraph, as a further contribution to the classification of our knowledge concerning the important symptom of jaundice.

SURGERY

UNDER THE CHARGE OF

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Acute Bowel Obstruction.—WANGENSTEIN (*Minn. Med.*, 1931, **14**, 16) says that the establishment of true criteria of bowel obstruction early in its course, will help more than any single factor in bringing patients to operation at an advantageous hour and to a definite lowering

of the present appalling mortality of the disease. Our textbook descriptions of intestinal obstruction should be labeled "Antemortem Signs of the Disease." They do not indicate interference with the continuity of the intestinal lumen, but herald impending dissolution. Regurgitant vomiting and distention must cease to be criteria awaited before a diagnosis can be made. Collapse in simple bowel obstruction should be relegated to the delineation of that antemortem status, in which all vital functions rapidly depreciate and from which escape or resuscitation is unlikely. Intermittent crampy pain, accompanied by nausea and considerable vomiting without abdominal rigidity or tenderness, is strongly suggestive of an acute block in the continuity of the intestine. The detection of loud intestinal noises on auscultation of the abdomen and the Roentgen ray visualization of gas in the small intestine, lend sufficient proof to make the diagnosis. The continuance of colicky pain despite the return of gas and feces on the administration of enemas, constitutes sufficient indication for immediate intervention.

Multiple Myeloma.—Coley (*Ann. Surg.*, 1931, **93**, 77) believes that the prognosis in multiple myeloma is by no means so hopeless as is universally believed. Most cases of multiple myeloma of both the ordinary and the solitary varieties are extremely sensitive to both the toxins of erysipelas and Bacillus prodigiosus and to radiation. In a number of cases the disease has been held in check for a very considerable period of time by the toxins alone or radiation alone, or by a combination of both agents. In 4 cases, 2 treated by toxins alone, 1 by toxins and radiation, and 1 by radiation alone, respectively, the disease has apparently been eradicated and the patient has remained well for a sufficient length of time to justify the hope of a permanent cure. No case of multiple myeloma should be given up as hopeless, without a prolonged trial of both toxins and radiation.

THERAPEUTICS

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Pernicious Anemia and Blood Transfusion.—Don (*Brit. Med. J.*, August 23, 1930, p. 280) believes that there is a real danger in neglecting older methods of treating pernicious anemia. He claims that in the presence of fever the patient may fail, or respond but slightly, to raw liver, cooked liver or to liver extract. In such cases timely blood trans-

fusions may yield excellent results. The author has administered repeatedly 500 cc. of blood to patients with a temperature of 102° F. who were suffering from pernicious anemia, with no untoward effect.

The Action of Insulin on Gastric Secretion.—In view of the contradictory reports of previous investigations, MEYER (*Klin. Wchnschr.*, 1930, **9**, 1578) undertook a carefully controlled study of the influence of insulin on gastric acidity and secretion in a variety of patients. He finds that in essentially normal individuals a dose of about 8 units of insulin subcutaneously or 6 units intravenously produces a constant increase of gastric acidity of pronounced degree which reaches its maximum in from seventy-five to ninety minutes. Along with this the majority of patients show an increase in the volume of gastric secretion. This action is shown to be specific for insulin and not due to its protein content. The action is also proved to be an early symptom or an actual side action of the hypoglycemia produced by insulin, there being a strict parallelism between the elevation of gastric acidity and the depression of blood sugar. Patients with diabetes fail to show gastric hyperacidity from insulin unless the dose is sufficient to induce hypoglycemia and in all diabetic patients the gastric effects of insulin are less marked than they are in normal individuals. Insulin is at least as effective as histamin in separating patients with total achylia from those with partial achylia, if not even more effective. From these studies it is evident that insulin is contraindicated as a means of improving nutrition in those patients suffering from hyperacidity, while on the other hand it is specially suitable for those with subacidity and anorexia.

The Circulatory Action of Sympatol.—TRENDELENBURG (*Deutsche medizinische Wochenschrift*, 1930, **56**, 1987) reports upon a series of pharmacologic experiments with a new substance very closely akin to adrenalin. This new substance called sympatol is chemically para-oxyphenylæthanolmethylamin, differing from adrenalin only in the absence of one hydroxyl group in the metaposition. The drug has properties closely similar to those of adrenalin, namely, the ability in adequate doses to cause an immediate rise of systemic blood pressure to the same degree as is produced by corresponding, though much smaller doses of adrenalin. The rise in pressure, like that from adrenalin, lasts only a few minutes. The dose of sympatol required to produce an equivalent action to adrenalin upon the blood pressure is from 60 to 100 times as great as that of adrenalin. From animal experiments Trendelenburg finds that sympatol differs significantly from adrenalin in the fact that, along with the rise in blood pressure, it does not produce an increase in intraäuricular pressure as is so characteristically the case with adrenalin. On the contrary, there is often a considerable drop in intraäuricular pressure during the period when sympatol is maintaining a high systemic blood pressure. Further, sympatol has no tendency to bring about marked irregularity in auricular contractions and when these are produced by a previous dose of adrenalin, the administration of sympatol is capable of checking them immediately. Sympatol also has very little tendency to produce premature systoles From a study of the simultaneous curves, it seems as though sympatol both increased the power of the muscular contraction of the heart at

the same time that it caused vasoconstriction with a rise of the systemic pressure so that a favorable balance was maintained between cardiac efficiency and peripheral pressure. In addition to the foregoing, sympatol exerts its actions after oral administration. The author believes that this new drug may prove to be an advantageous substitute for adrenalin and one that is free from harmful effects of the older drug.

Simultaneous Bilateral Artificial Pneumothorax in the Treatment of Pulmonary Tuberculosis.—The induction of bilateral pneumothorax in patients with tuberculosis is a rather recent therapeutic experiment. COULARD (*Ann. de méd.*, 1930, **28**, 320) presents a clinical and statistical analysis of this therapeutic procedure after treating 116 cases. Because the pulmonary tuberculosis is usually more advanced in cases in which this procedure is used than in cases in which unilateral artificial pneumothorax is applied, the results of bilateral pneumothorax cannot be expected to be as favorable. The author's analysis indicates that, although a considerable percentage of the patients who were treated by this method died, a group of patients survived who doubtless would have succumbed without treatment. It is suggested that the beneficial effect of double pneumothorax would be increased if the indications outlined by the author were followed. The treatment should be considered as a major therapeutic procedure with great potential danger. This measure should be applied cautiously and only by those who have acquired considerable experience in the technique of unilateral pneumothorax.

PEDIATRICS

UNDER THE CHARGE OF

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Postvaccinal Encephalitis in Infancy.—SCOTT (*Brit. J. Dis. Child.*, 1930, **27**, 245) reports a new case of postvaccinal encephalitis in infancy and quotes 21 other cases. These cases seem to fall into five clinical groups. The cerebrospinal fluid was found to be normal in almost every case. In this series as opposed to other series there was no particular day after vaccination on which the majority of cases occurred. Postmortem examination on one of this series showed lesions scattered through the central nervous system, with the chief incidence in the thoracic region particularly about the anterior roots of the ninth dorsal segment. The case showed wide areas of demyelization, with the histologic appearance characteristic of the subacute case. This condition must be differentiated from the various forms of meningitis, subarachnoid hemorrhage, from any of the usual causes of convulsions, tetanus and strychnin poisoning, acute encephalitis lethargica and poliomyelitis. The prognosis depends largely on the clinical type of the disease. The condition is much more rare in infancy than at other age periods.

The etiology is extremely obscure and at present no explanation is offered of all the conflicting experimental evidence. The virus may be the vaccinia virus alone acting in a poor soil. There may be an as yet unknown virus which attacks only those whose constitution has been altered by vaccination. The virus may activate another virus, either known or unknown, which is lying dormant in the individual vaccinated. It may be the expression of an allergic phenomenon.

Incomplete Dilatation of the Lungs as a Factor in Neonatal Mortality.—HENDERSON (*J. Am. Med. Assn.*, 1931, **96**, 495) states that the natural stimulus initiating breathing in the normal child at birth can now be stated to be the carbon dioxid produced in its own body. While physiologic theory for many years has suggested this view, the objection could not be overcome that a nonbreathing child probably has a higher pressure of carbon dioxid in its blood than one that breathes spontaneously. He shows that the asphyxiated respiratory center of the newborn, or of a drowned person, requires a much higher pressure of carbon dioxid than does a normal center to stimulate it to respiratory activity. For the asphyxiated newborn child, dilatation of the lungs with a mixture containing a sufficient amount of carbon dioxid in oxygen to stimulate natural breathing is the only one really effective method of resuscitation. This amount is 7 per cent of carbon dioxid in 93 per cent of oxygen and the mixture is called "carbogen." Inhalation of this mixture is equally important for many children that breathe spontaneously, for among these there are many cases of incomplete dilatation of the lung, which predisposes to pneumonia and which causes as nearly as high a mortality as stillbirth. This inhalation should be administered therefore not only to those infants who require it for resuscitation from asphyxia but to all children, even to those who appear entirely normal, during the first few days of life as a prophylaxis against continuing partial atelectasis, secondary asphyxia, and pneumonia. The author feels that apparatus for the administration of this combination should be in every maternity, and that for deliveries in private homes that the apparatus should be available for rental at a nominal price to cover the gas used. He feels, further, that after a reasonable period of education that all obstetricians and midwives be held by legal requirement to utilize this method in a manner similar to the requirements for prophylaxis against blindness.

Intraperitoneal Iron.—GRULEE and SANFORD (*Am. J. Dis. Child.*, 1931, **41**, 53) injected 5 cc. of colloidal iron as ferric hydroxid, the solution containing 8 mg. of colloidal iron. This standard amount was used irrespective of the weight of the child and was administered twice a week for eight injections. Little or no rise in the hemoglobin or the red cells was seen during the period of injections or about thirty days. Following this time there was observed a rise of hemoglobin to the amount of 5 per cent a week. It is the general idea that secondary anemia is due more to an inability to use the iron taken in or stored in the body than to a mere lack of iron. The administration of iron, therefore, simply creates a reservoir store on which the body may draw. In this series all of the patients received ultraviolet irradiation to assist the body in its assimilation of iron. Their method of irradiation

was to expose the front and the back of the body, beginning with a three-minute exposure and increasing the time one minute a day until an exposure of ten minutes was given. Irradiation was then stopped. The children were kept in the hospital for one month and then returned for blood check-up monthly. In this series no effect or reaction was noted with the dose given. This form of treatment is recommended only in cases of secondary anemia.

A Survey of Tuberculosis in Schools in Colorado.—VERPLOEG and BAZEMORE (*Am. J. Dis. Child.*, 1931, **41**, 26) state that the statistics for the mortality and morbidity of tuberculosis in children today and ten years ago are not comparable. The number and size of positive reactions increase in children commensurate with contact and age. The incidence of tuberculous infection among children varies greatly in different parts of the country, and is influenced by climatic and other environmental factors. A survey for tuberculosis in the school of a small community, composed largely of health seekers, when contact with the disease is unusually great, showed 36.4 per cent of 283 children from four to fifteen years of age to be infected. This is only a moderate increase over the incidence noted in nontuberculous communities. Roentgen studies of the 103 children giving positive reactions revealed childhood tuberculosis in 19 or 6.7 per cent of the whole group, the average for the country at large varying from 1 to 4 per cent. No child was found with the adult or exudative type of tuberculosis. Most of the children reacting positively and those having actual childhood tuberculosis were not natives of Colorado. Climatic factors in this state apparently exert a favorable influence in the protection of children against active tuberculous infection. In this study the father was the source of the infection in 64.8 per cent of the children giving positive reactions and the mother in only 12.6 per cent. The authors feel that the symptoms of fatigue, undernutrition and a history of frequent colds are not reliable aids in the diagnosis of the disease.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Clinical Characteristics, Bacteriology and Etiology of Ulcus Acutum Vulvæ.—This by no means uncommon condition, frequently confused with venereal ulcerations, is discussed by ROSENTHAL (*Arch. f. Dermat. u. Syph.*, 1930, **162**, 95) from the standpoint of the rôle of Bacillus

crassus in the etiologic picture. He is inclined, as a result of his studies, to accept the suggestion of Lipshutz, that this apparently benign saprophytic organism in certain predisposed patients may give rise to these acute outbursts of genital ulceration, known as ulcus acutum vulvæ. The author suggests the necessity for an investigation of the allergic response of these patients to Bacillus crassus, and believes that in such an allergic response may be found the explanation of this severe ulcerative reaction in certain individuals to the presence of what is ordinarily considered to be a saprophytic organism.

Dermatomyositis Pseudoleukemica.—URBACH (*Arch. f. Dermat. u. Syph.*, 1930, **162**, 27) reports what he believes to be a new dermatologic picture associated with important constitutional manifestations. The patient presented a dry, reddened and scaling condition of the skin, followed by edema of the extremities and the nasal region and later by extensive purpuric hemorrhages. Deep pigmentation subsequently appeared, brownish-red and violaceous nodules developed over the body, and those regions not thus affected presented a picture suggesting poikiloderma vasculare Jacobi. There was enlargement of the palpable lymph nodes, and upon histologic examination the corium was found to be the seat of a round-cell infiltration over practically the entire body. A typical leukocyte count was 11,000, with a relative leukocytopenia, an absolute eosinophilia of 10 to 15 per cent and a monocytosis of approximately 15 per cent, with a slight increase in lymphocyte count. Ulcerated and crusted lesions appeared during the course of the disease. Specimens of excised muscle showed extensive infiltration with lymphocytes. The patient developed an exophthalmos, evidence of labyrinthine involvement and impairment of vision resulted from herpetiform changes in the cornea. The lymphatic enlargement responded to Roentgen ray therapy, but the cutaneous picture remained comparatively unchanged over a period of many months. The author believes the condition to be an infectious or toxic dermatomyositis, and discusses the differentiation from mycosis fungoides and the well-recognized lymphomatoses of the skin.

GYNECOLOGY AND OBSTETRICS

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Treatment of Salpingitis With Turpentine.—An atmosphere of enthusiasm pervades the report of LITTLE (*Am. J. Obst. and Gynec.*, 1930, **20**, 582) on the use of turpentine injections in the treatment of gonorrheal salpingitis. He has been able to obtain permanent relief of pain in 90 per cent of the patients without the removal of ovaries and in the vast majority of the cases the inflammatory masses disappeared in from

four to six months. His method consists of opening the abdomen, protecting the peritoneum by rubber sheeting and releasing the adhesions about the adnexa. Tubal masses are evacuated by means of a syringe with a fairly large needle, after which the syringe is changed and the same needle used to inject a variable quantity of 10 per cent turpentine in oil. No attempt is made to prevent the solution from exuding into the pelvic cavity. The uterus is then suspended with silk either by the Olshausen or Baldy-Webster method. While the exact method of operation of these injections remains doubtful, in a number of cases very profuse uterine discharge was noted three to four days subsequent to the injection suggesting that an obstruction of the lumen of the tube at the uterine end had been overcome. It is certain that the oil does not remain in the tube as in one instance, a later operation revealed that the tube contained a limpid fluid which was negative to tests for oil and turpentine. It is the Reviewer's opinion that in the very great majority of patients suffering from gonococcal pelvic inflammatory disease, a very satisfactory result can be secured under the influence of heat and time, allowing plenty of the former and more of the latter.

A Statistical Study of Maternity Care.—The report made by DUBLIN and CORBIN (*Am. J. Obst. and Gynec.*, 1930, **20**, 877) covers a study made jointly by the Maternity Center Association and the Statistical Bureau of the Metropolitan Life Insurance Company of the records of 4726 women cared for by the Association during the past eight years. It is significant that during this entire period only 28 per cent of the patients came under observation before the fifth month of pregnancy. About an equal number of the women were delivered at home and in hospitals. Considering all the cases together, physicians attended slightly more than three-quarters of the cases, Bellevue Midwife Service 17 per cent and other midwives 7 per cent. The following concrete results of these 4726 pregnancies are of interest: (1) During the entire period of eight years no woman under care died before delivery; (2) eleven mothers died after delivery from puerperal causes; (3) there were 4596 live born babies, 123 stillbirths, and 132 of the live babies died before they were one month old; (4) there were 274 premature deliveries, 61 of which were miscarriages. It was gratifying that no death occurred from eclampsia, for when all is said and done, the deaths thay may surely be prevented by supervision during pregnancy are those which result from the toxemias and from bleeding during pregnancy. This study demonstrates that, on the score of all essential indices, prenatal care, as conducted by the Maternity Center Association, produces effective results. The mortality of the mothers was reduced to about a third of the mortality occurring in the same area among women not receiving intensive care. Stillbirths were 42 per cent lower than in the rest of the district and infant deaths in the first month of life were reduced 32 per cent as compared with the control group in the same area. For the country as a whole, the results achieved in the Maternity Center experiment reported in this study, have very definite implications. If the same type of service could be rendered universally, 10,000 of the 16,500 women who die annually could be saved; many stillbirths could be prevented and some 30,000 babies that annually now die, under one month, would be living.

Vesical Diverticulum in the Female. Diverticula of the urinary bladder are infrequently found in the female as evidenced by the report of SCHACHT and CRENSHAW (*J. Urol.*, 1930, **24**, 393) who found only 18 cases in females over a period of nearly twenty years in the Mayo Clinic, the ratio in females and males being approximately 3 to 97. In the series reported 13 were true and 5 were false diverticula. In 3 cases a urethral caruncle was present, in 1 case a cyst 1.2 cm. in diameter was found at the neck of the bladder. Of the false diverticula, 1 was the result of injury at childbirth and the other 4 were the results of operative procedures in the pelvis and abdomen. The symptoms of this condition are usually in proportion to the associated infection of the bladder and complications such as vesical calculus or neoplasm of the bladder. The diagnosis can practically always be made by means of cystoscopy and cystograms.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Eye Changes Observed in Paretic Patients After Treatment With Malaria.—CLARK (*Am. J. Ophthal.*, 1930, **13**, 946) examined the eyes of 50 patients before and after treatment for paresis by inoculation with malaria. The patients presented clinical signs of paresis as well as positive Wassermann reaction on the blood and spinal fluid. The majority of the patients had received treatment for syphilis prior to the onset of the psychosis. "After admission to the hospital, no treatment was administered for syphilis except therapeutic inoculation with benign tertian malaria. Therefore, it is assumed that the eye changes, noted after the malarial fever had subsided, were brought about by the malaria." Observations were made on central visual acuity, extraocular motor anomalies, pupillary phenomena, eye-ground changes, and visual fields. Improvement in central visual acuity was judged by comparison of tests made with whatever corrective lenses the patient had, no attempt being made to elicit the best acuity by refraction. The vision of twenty-five eyes was improved one to two lines on the chart. There was no marked improvement recorded in any one. A patient with optic atrophy showed no improvement. Six patients were found to have unilateral Argyll-Robertson pupils. All 6 recovered the normal pupillary reaction of the affected eyes within three months after the malaria was arrested. Twenty-eight patients had bilateral Argyll-Robertson pupils, 22 of whom regained normal pupillary reaction after malaria was terminated. The pupils of 6 patients were not improved by the malaria treatment. Definite pathology in some portion of the fundus was found in the eye of 22 patients. There were 8 with floating opacities of the vitreous body. During the height of the

fever there was a decided congestion of the nerve head and blurred disk margins, particularly of the nasal and upper portion and engorgement of the retinal vessels as shown by increased caliber, tortuosity, and prominence of the small vessels. After malaria subsided 12 of the 22 patients showed a decided improvement, manifested by an improved color of the disks. One patient developed neuroretinitis with the administration of quinin, which subsided when quinin was discontinued. The inflammation was thought to be due to the drug. Four patients showed improvement in the perimetric fields.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Sensitivity on Palpation of the Eyeball as a Symptom of Sinus Disease.—ZYTOWITSCH (*Bericht über den 3. Kongress der Aerzte Mittelasiens*, 1930; abstr., *Klin. Monatsbl. f. Augenh.*, 1930, **85**, 310; abstr., *Arch. Otolaryng.*, 1930, **12**, 537) states that pressure from above downward causes an increased sensitivity of the eyeball in maxillary sinusitis. The same symptom can be elicited in ethmoiditis when the eyeball is pressed inward and in sphenoiditis when it is pressed backward. The ocular sensitivity is more marked in the chronic types of sinus disease.

Medical Therapy in Otosclerosis.—The inability to arrest the progress of deafness and tinnitus aurium in otosclerotics is one of the most discouraging chapters in otology. Desperate efforts to lighten the burden of these unfortunates have resulted in a therapeutic armamentarium as extensive as it has been unavailing. Many drugs and biologic products—notably iodin, phosphorus, calcium, bromin and hormonal preparations—have met with no greater success than the host of mechanical and electrophysical procedures that have been tried. Recently, BIRKHOLZ (*Monatschr. f. Ohrenh.*, 1930, **64**, 558) reports the failure of viosterol to alter the course of otosclerosis. However, he offers a faint ray of hope in the systematic intravenous administration of calcium bromid to cases of moderate severity.

Experimental Investigations Concerning Selective Localization of Bacteria, Particularly in Relation to Affections Secondary to Tonsillar Disease.—The importance of focal infection as a principle of infection in numerous disease processes in man cannot be taken lightly. The factors determining the localization of bacteria have been the basis of extensive study and much controversy for over fifteen years. Largely as a result of a desire to ascribe each infectious process to a specific bacterial cause, much emphasis has been placed on the microörganism as the exclusive agent in infectious diseases. One of the most popular hypotheses advanced to explain the occurrence and incidence of focal

infection is known as "elective localization" and implies an inherent property in the bacterium to successfully invade specific tissues and organs. That some microbic forms have a certain degree of natural selectivity for particular structures is well known—as, for instance, the meningococcus and the gonococcus. Furthermore, a certain general bacterial adaptation to environment is accepted by every one. But, without minimizing the importance of bacterial specificity, it would appear that the factors on the side of the host are more variable and far more important than those having to do with the microbes themselves. In endeavoring to ascertain whether bacteria, isolated from tonsils of patients exhibiting focal lesions in particular viscera, selected the same organs when injected into animals, HESSE (*Ztschr. f. Hals-, Nasen-u. Ohrenh.*, 1930, **26**, 198) could not demonstrate any constant ratio between the incidence of visceral lesions occurring in the host and those produced in the experimental animal.

RADIOLOGY

UNDER THE CHARGE OF

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Coarctation of the Aorta.—A review of the diagnostic features of coarctation by FRAY (*Am. J. Roent. and Rad. Therap.*, 1930, **24**, 349) revealed two findings which may be considered pathognomonic: (1) A defect in continuity of the arch at the junction of the transverse and descending portions of the aortic arch as outlined in the left posteroanterior oblique view; (2) with erosions which may be identified in either the oblique or posteroanterior view. Rib erosion, when present, may be considered practically pathognomonic, but its absence does not rule out coarctation. Absence of the aortic knob in an adult, posteroanterior view, is highly significant. Left ventricular hypertrophy and dilatation of the proximal aorta are usually present, but they are also noted commonly in various other cardiovascular disorders.

Factors Determining Ultraviolet Dosage and Course of Treatment.—WARNSHUIS (*Arch. Phys., Therap., X-ray, Radium*, 1930, **11**, 532) believes that the amount of ultraviolet irradiation at each treatment should be determined by the character of the clinical response to one erythema unit of radiation and subsequent increases rather than by the degree of skin reaction. In the absence of insomnia, lack of clinical improvement and severe focal reactions the intensity of radiation can be increased gradually to a maximum of 5 to 8 erythema units. Two or three days should elapse between exposures. In cases that react well four to five irradiations may suffice to restore normal intermediate

metabolism. Most cases with symptoms of vitamin deficiency becomes stationary after a month of treatment insofar as their response to ultraviolet radiation is concerned, and for practical purposes treatment may be interrupted then until indications of a relapse appear.

Radium in the Treatment of Toxic Goiter.—Radium is highly effective in controlling hyperthyroidism, including the diffuse exophthalmic type as well as that associated with adenoma, in the view of LOUCKS (*Am. J. Roent. and Rad. Therap.*, 1930, **24**, 280). Results with radium parallel those with surgery; the type of case that responds poorly to radiation is the type which requires two or more thyroid operations. Radium therapy accomplishes a marked restoration of sugar tolerance in cases associated with glycosuria, indicating a complete control of the hyperactive thyroid. The primary mortality is *nil*, pre-operative and post-operative morbility is eliminated; from the standpoint of the period of disability, hospital expenses and the concomitant loss of wage-earning power, radium holds a tremendous economic advantage over any other therapeutic procedure. In the same issue (p. 283) GINSBURG holds that radium therapy, efficiently used, relieves not only the toxic but also the compression phenomena in toxic adenomatous goiter. He claims also that radium and Roentgen therapy efficiently employed has yielded results superior to operation in the treatment of primary and metastatic thyroid cancer. Discussing the foregoing papers, ROBINSON (p. 298) said that his experience with a considerable number of these patients had not been entirely pleasing, because of the difficulty in reducing the size of the thyroid. Even though patients are told that their necks will not go back to normal, they nevertheless expect it. He has seen skin changes in some of the cases and even with moderate doses of radium. It is disfiguring, to say the least, and whether or not a smooth scar is preferable to these changes is for the profession to decide. It seems to him that surgery of the thyroid has been so uniformly successful that with the pitfalls and difficulties in reducing the tumor with radium, irradiation may not be the treatment of choice. In the treatment of malignant disease of the thyroid he thought that all had obtained excellent results by a combination of surgery and radium.

Healing in Bone Tuberculosis.—In the experience of HANSON and FENGER (*Radiology*, 1930, **15**, 374), healing by production of osseous tissue occurs in bone tuberculosis and is more prevalent in tuberculosis of the vertebræ than in the hip or in sacroiliac involvement. This is contrary to the teaching that there is no new bone formation in tuberculosis. It has also been taught that loss of the intervertebral space, accompanied by lipping and spur-formation on the edges of the vertebræ is pathognomonic of arthritis deformans, but the authors have observed these phenomena in 15 per cent of proved cases of Pott's disease.

Gastrointestinal Obstruction.—Roentgenologic examination is considered by BROWN (*Radiology*, 1930, **15**, 364) to be an excellent method by which obstruction of any degree can be diagnosed without difficulty. He deplores the fact that the Roentgen ray is frequently not called upon for aid and patients who might be saved are sacrificed. He

emphasizes the point that the most serious cases of obstruction, such as the acute form which is responsible for the usual high mortality, can be recognized even on a plain Roentgen ray film of the abdomen. The obstruction is manifest in the distention and reticulation of the small bowel. In other cases the barium meal or enema can be used. The author insists that neither has ever caused harm to patients.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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The New Mexican System of Criminology.—MENDOZA (*Journal of Criminal Law and Criminology*, 1930, **21**, 15) reviews the origin and provisions of the new Mexican code. He states that this code is inspired by the attitude that it is not necessary for society to be angry and bitter against criminals in order to keep the welfare of the community. "In drafting this new penal code we did not need to go, however, so far as to establish that all of the criminals are sick people, as some observers of the Mexican criminology have asserted. It was enough to assume, that criminals are dangerous beings for the common interests of society, for dealing with the problem. Nevertheless it seemed to us that society would have a better chance to combat the evil of crime, if it could acquire something like the coldness and simplicity of physicians and surgeons when they cut and cure." For this reason, an attempt was made to get completely away from the implication of pain, anger or revenge. Since the responsibility for crime rests as much or more with society than with the individual, he contends that it becomes the duty of society to put a stop to it since the individual has not control of the situation. It was felt that a new attitude of treatment toward the offender should accomplish more in this direction than the older methods. The reason for abolishing capital punishment, he states, was the logical conclusion arising from this premise, that if treatment was to be instituted it would not be proper to kill people only because of the failure of society in finding better means to defend itself against them. Because of the highly specialized character of this work, the drafters of the code abolished the jury system and instituted in its place a specialized board, designated as a "Supreme Council of Prevention and Social Defense." To this board have been appointed five eminent specialists in the fields of criminology, anthropology, sociology, law and psychiatry. There follows a description of Mexican publications dealing with the new method.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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A Contribution to the Study of the Pathogenic Relation Between Acute Leukemia and Septic Infection.—Bonciu and Ionesco (*Arch. Roumaines de path. expér. et de microbiol.*, 1930, **3**, 65) have given a brief résumé of the literature on this subject. For many years many writers have advanced the theory that the picture seen in acute leukemia was due to acute infection with the streptococcus usually named as the causative agent. The converse theory has also been advanced —that leukemias have a lessened resistance to the organism. The authors have presented a case of a little girl, who following repeated sore throats developed a syndrome fairly typical of beginning acute leukemia. In three weeks here red cell count fell from 3,180,000 to 1,760,000, her white count from 18,600 to 2600 and her platelets from 210,000 to 140,000. Mononuclear cells with numerous lymphoblasts dominated her white blood picture. A strongly hemolytic streptococcus was isolated from her blood stream during the acute phase. She ultimately rallied well following several transfusions of her mother's blood (her red cell count rose to 4,160,000 and her white count to 16,000) and her blood culture became sterile. Later, however, she suffered an exacerbation and died, four months after the onset. Autopsy was not performed. It was the belief of the authors that they were dealing with an aleukemic leukemia and that the presence of the streptococcus was in the nature of the secondary invasion dating back to her tonsillitis. The presence of the immature cells in her blood stream they believed to be due to the leukemia and not to the septicemia.

On Certain Possible Causes of Error in the Signs Given by the Biologic Reactions of Cerebrospinal Fluid.—Goresco and Popesco (*Arch. Roumaines de path. expér. et de microbiol.*, 1930, **3**, 95) observed a series of 5 cases which were admitted to the Queen Elizabeth Military Hospital for Contagious Diseases during 1928 and 1929, in each of which cerebrospinal serology seemed to point to a diagnosis of syphilitic meningitis, but the subsequent course of the disease proved this to be fallacious: (1) Onset of disease four days before with chills, headache and neck rigidity, presenting photophobia, marked Kernig's sign and elevation of temperature; one sample of cerebrospinal fluid gave positive Bordet-Wassermann, but others were negative and the patient made a complete recovery. (2) Onset with polyarthritis, fever, epistaxis. Subsequently developed a left lobar pneumonia. During convalescence the recurrence of fever, coupled with cerebrospinal signs led to a diagnosis

of syphilitic meningitis—the spinal fluid giving a positive Bordet-Wassermann. The ultimate diagnosis, however, was dementia precox. The 3 remaining cases were similar to the above, all presenting cerebrospinal syndrome with positive spinal fluids. One died and autopsy revealed a tuberculous meningitis. Both the others progressed to complete recovery. It was concluded that the temporarily positive findings were due to acute transient febrile states. The authors emphasized the necessity for repeating spinal fluid serology in this type of case with a view to avoiding similar errors in diagnosis.

On An Epidemic of Enterocolitis Caused by a Salmonella.—A study was made by BALTEANU, CALALB, ALEXA and ECSTEIN (*Arch. Roumaines de path. expér. et de microbiol.*, 1930, **3**, 5) of the various phases of an epidemic of enterocolitis which invaded several villages in the district of Jassy and neighboring communities, beginning early in July, 1929, with a few scattered cases confined to the age group of from one to ten years, and lasting until August 15, 1929. It eventually involved adults as well as children. A marked exaltation of virulence was noted, the early cases being mild in type while the ultimate mortality was 10.4 per cent. The disease was at first ascribed to a dysentery bacillus, but serologic research disproved this and the pathogenic agent was identified as belonging to the Salmonella group. Concurrently with the onset, an epidemic broke out among the cattle of the districts affected, characterized by gastrointestinal manifestations and an exceedingly high mortality. No conclusive research was done. All patients complained of severe diarrhea (forty to sixty movements per day), loss of appetite and general malaise. Blood cultures were consistently negative. Vaccine therapy was employed with complete success. There were no deaths among those who had undergone a complete vaccination. In all, 258 cases occurred in a population of 2849, with 27 deaths.

Lesions in the Joints by Various Bacteria.—The localization of bacteria about and in the joints has been the subject of a great deal of experimental research, and the evidence has been accumulating that the factors determining the localization of bacteria from the blood stream are those which alter the circulation and thereby the nutrition of the cells of the tissues, especially the endothelium of the capillaries. The production of joint lesions in rabbits after intravenous injections by members of the lactobacillus group of both dental and intestinal origin by HOWITT and VAN METER (*J. Infect. Dis.*, 1930, **46**, 368) and by HOWITT (*J. Infect. Dis.*, 1930, **46**, 491), using M. gazogenes (Lewkowicz) brings newer evidence that the joint lesions in rabbits are more a function of the circulatory system of the invaded host than of an inherent elective localization of the bacteria involved.

Sodium Salicylate and Intradermal Reactions.—The actual site of the therapeutic action of sodium salicylate is not as yet precisely determined. Many think the good results in such diseases as rheumatism are due primarily to the effect on the capillary circulation. The investigation by HAGEBUSH and KINSELLA (*Proc. Soc. Exper. Biol. and Med.*, 1930, **27**, 922) showed that sodium salicylate effectively suppressed the so-called allergic reaction to filtrates of a strain of Strepto-

coccus hemolyticus. The cultures of the streptococcus intra-articularly had produced a persistent purulent arthritis without blood-stream infection unless an intercurrent disease such as "snuffles" intervened. Intradermic reactions to a filtrate were always present ten days after this arthritis had been established. Intravenous treatment with sodium salicylate before the induction of arthritis and at twenty-four-hour intervals thereafter suppressed this intradermic reaction. Glycin given alone had no effect and when injected with the sodium salicylate prevented the suppressive action of the latter. The authors do not believe the effect is due to vascular changes because the sodium salicylate does not affect the nature of the vascular pathology found in these rabbits. The late proliferative vascular lesions were the same in the various series. (The late vascular changes may have little bearing on the vascular and cellular response to the antigens from the arthritis focus in the course of developing allergy. See retrospects of DIENES' studies (*Proc. Soc. Biol. and Med.*, 1930, **28**, 72, 75.)

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Epidemiology of Tuberculosis in New York City.—DROLET (*J. Prev. Med.*, 1930, **4**, 115) states that the tuberculosis death rate in New York City is still high, particularly among certain groups: Among women twenty to twenty-five (106 per 100,000); among men sixty to seventy years (256). In certain sanitary areas on the East Side and in the Harlem District, the rate still exceeds 300. In the thirty-year period 1898–1927, the general tuberculosis death rate in New York declined from 282 to 86, a fall of 70 per cent. Since 1921 the rate has tended to remain at about 90, due to conflicting influences, largely economic and racial. Tuberculosis in New York City kills about 60 men to 40 women. Since 1920 in New York City the greatest decline in the tuberculosis death rate has occurred among children, with a reduction of 45 per cent among those under fifteen years of age. Among young women fifteen to twenty years of age the rate has fallen by 29 per cent, and among those twenty to twenty-five by 36 per cent. There has been no increase lately in the tuberculosis death rate of young women in New York City, but instead a marked reduction exceeding that of young men particularly at ages between twenty and thirty years. The crest of female tuberculosis mortality is now at a lower level than formerly. It is reached, however, at an earlier age period. While in 1910 it occurred in the thirty to thirty-five age group, in 1928 it was

at twenty to twenty-five years of age. Among males, the greatest reduction (57 per cent) during the period 1920–1928 occurred at ages five to ten. The peak in the mortality of the male sex, formerly found between the ages of forty-five and fifty, now occurs between the ages of sixty and seventy. During the period 1898 to 1928 the infant tuberculosis death rate has fallen by 88 per cent. Among children under fifteen, the rate has declined from 136 to 27, or by 80 per cent. Since 1920 there has been a reduction of 45 per cent in the latter group. In a given 1000 tuberculosis deaths in New York City at the present time the age concentration among females is at twenty to twenty-five years; among males, at forty to forty-five; among Negro males at twenty-five to thirty, and white males at forty to forty-five; among both Negro and white females at twenty to twenty-five; among Jewish males after forty-five. In 1868 in New York City there were two peaks of tuberculosis mortality in both sexes: among young children and after the age of sixty-five.

Brucella Abortus in Certified Milk.—Hasley (*J. Infect. Dis.*, 1930, **46**, 430) reports the results of investigations showing that it is possible to detect *Bacillus abortus* in market certified milk by plating methods. *Bacillus abortus* was grown from 10 of 230 samples examined; the 10 positive samples were obtained from 3 of the 5 dairies studied. The highest number of organisms found was 8 per cc. of milk; the average for the 10 positive samples was 2 per cc.

Immunity to Poliomyelitis in Mothers and the Newborn as Shown by the Neutralization Test.—Aycock and Kramer (*J. Exper. Med.*, 1930, **52**, 457) performed neutralization tests for the virus of poliomyelitis on blood serum of urban mothers and their newborn infants and found immunity to be present in 10 out of 12 (83 per cent) infants and in 10 out of 12 (83 per cent) mothers, with a complete correspondence between mother and infant. The authors state that these tests point to passive transmission of immunity from mother to infant. Previous tests on other children (one to five years) indicate that immunity in infants is transitory. Previous observations concerning the extent of immunity in urban adults are confirmed and extended. The results of these tests are in accord with the age distribution of poliomyelitis and parallel corresponding observations in diphtheria.

The Heat Resistance of the Virus of Poliomyelitis.—Shaughnessy, Harmon and Gordon (*J. Prev. Med.*, 1930, **4**, 139) state that the exact thermal inactivation point of poliomyelitis virus apparently cannot be determined at the present time because there is no accurate method for standardizing the potency of virus preparations. The results reported suggest that, when a small amount (2 cc.) of a virus of moderate potency is used, the thermal inactivation point is quite low, about 42.5° C. for thirty minutes. On the other hand, in one experiment the temperature necessary to produce inactivation was higher than 50° C. for thirty minutes, due probably to chance variation in the strength of the virus preparation. In other similar experiments a temperature of 55.5° C. for all periods of from five to thirty minutes always produced inactivation of the virus. This accords with the results of other inves-

tigators. When large amounts of a virus of moderate potency were used, the thermal inactivation point was 52.5° C. for thirty minutes. Apparently an increase in the amount of virus injected caused the difference in the effect upon monkeys. These results suggest that at temperatures slightly above 40° C. (42.5°) the virus is possibly attenuated or, more probably, that part of the virus is destroyed so that a relatively small inoculum becomes ineffective in producing clinical poliomyelitis. Furthermore, virus which is innocuous in a single injection may produce clinical symptoms of poliomyelitis on repeated injections.

Hygiene of the Towel.—PEASE and HIMEBAUGH (*Am. J. Pub. Health* 1930, **20**, 820) state that the common towel in public or in the home is an ever-present menace as a potential carrier of disease, producing organisms which thus may be easily transferred to the hands of each new user. Whether for drying the face, hands or entire body, the employment of an individual single service towel constitutes a wise precaution against excessive numbers of relatively harmless or of disease-producing contaminations by bacteria already on previously use towels. The Turkish towel is more efficient than the huck or the paper towel in removing bacteria and dirt from the skin.

The Seasonal and Regional Incidence of Types of Malaria Parasites.—BARBER and KOMP (*Pub. Health Rep.*, 1929, **44**, 2057) present the following summary: (1) In the southeastern United States there is a marked predominance among malaria cases in the white race of *vivax* in the spring months and of *falciparum* in the autumn. (2) In the colored race there is less indication of a seasonal incidence of types of parasites, but the incidence of *falciparum* is higher in all months than in the white race. (3) A large proportion of the cases present mixed infections of *falciparum* and *vivax* at some time during their history. (4) The greater resistance of *vivax* to treatment or to other antimalaria influence is probably the most important factor in determining the seasonal variations of *vivax* and *falciparum* in the white race and of the high incidence of *falciparum* in the colored. (5) *Falciparum* apparently has not become well established in the Rio Grande Valley of Texas and New Mexico. *Vivax* is the most predominant type there at all seasons of the year.

The Immunizing Value of Diphtheria Toxin-antitoxin Mixture and of Diphtheria Toxoid.—HARRISON (*Pub. Health Rep.*, 1930, **45**, 1883) discusses the merits of the preparations mentioned and makes the following conclusions: (1) In 475 school children diphtheria toxoid gave an immunity response, as measured by the Schick test, of 95 per cent as compared with 64 per cent in 355 children receiving 0.1 L+ dose toxin-antitoxin mixture. (2) No local or general reactions were reported in children receiving toxoid, those giving reactions to intracutaneous test injections of diluted toxoid having been removed from the group. (3) Two doses of 1 cc. each, with an interval of one month, produced a negative Schick reaction in a high percentage of subjects.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 16, 1931

Growth Changes in an Isolated Portion of the Spinal Cord in Birds.—Roy G. Williams (from the Laboratory of Anatomy, University of Pennsylvania). Isolation of the lumbar enlargement of chick embryos before it had been influenced by stimuli coming from other parts of the central nervous system was accomplished by removing the 19th to the 23d segments at fifty-six hours of incubation and placing a mechanical block in the defect. When such a chick hatched the legs developed a rigid paralysis in extension after twelve hours. When stimulated the legs responded bilaterally. Since the sympathetic system was intact and the animal gave an apparent pain response when stimulated over the legs, the possibility is suggested that in chicks some peripheral pain stimuli may reach the brain by way of the sympathetic nerves. Histologic studies indicated that the gray matter had been reduced in area by 13.1 per cent and the white matter by 43.9 per cent. The total number of cells was reduced by 41.4 per cent. Neither the size nor the shape, distribution, or arrangement of the cells present was significantly affected. There is a definite size relationship in the cells of the anterior horn in normal animals, and the relationship was unchanged under the experimental conditions. It is suggested that stimuli from caudally growing nerves regulate to a considerable extent the degree of cellular proliferation in the lumbar enlargement, but that the relations and morphological plan of the region are inherent in it.

The Spierer Lens and What it Reveals in Cellulose and Protoplasm.—William Seifriz (from the Laboratory of Botany of the University of Pennsylvania). Charles Spierer has applied a little known optical principle to dark-field illumination and obtained striking results. Spierer knew that a colloidal particle scatters more light *in the direction of*, that is, *away from the source of*, the illuminating ray, than in any other direction. He, therefore, reasoned that more would be seen if colloidal matter were viewed in a direction directly opposed to that of the illuminating ray, that is, toward the source of illumination. In order to accomplish this, and yet have a dark field, Spierer inserted a small metallic mirror in the lens system of an oil-immersion objective. In the early experimental work the mirror was of gold or aluminum foil; it is now of platinum and is "spattered" on from the cathode of a discharge tube. The mirror is smaller than the lens aperture yet reflects *all* the direct rays of light coming from below. The pencil of light from the source of illumination must be of a diameter not greater than the mirror; this is accomplished by having the aperture in the substage iris-diaphragm at least as small as the mirror. The lens, as now manufactured, is a Zeiss $\frac{1}{12}$ inch oil-immersion objective of 90× magnifica-

tion and is supplied with an adjustable iris of 1.25 mm. maximum and 0.8 mm. minimum aperture.

The ultramicroscopic structure of the cellulose walls of both dead and living plant cells is characterized by linear arrangement and discontinuity. The linear arrangement is of parallel striæ; the discontinuity is due to the presence of small rod-shaped particles oriented end-to-end. The striæ usually run parallel to each other with only occasional irregularities. The general arrangement of the striæ is often strikingly symmetrical. At times, the striæ run at right angles to or even cut diagonally across each other.

Protoplasm seen through the Spierer lens presents the picture of an emulsion when quiet but becomes much like cellulose when under a mechanical stress as when streaming or stretched into strands. The linear arrangement of rods in living protoplasm is, under favorable conditions, very marked. The rods are light gray in color (translucent) and the background black. The linear masses are separated from each other by distances shorter than their length, as in cellulose, and they retain their relative positions, even while the protoplasm is streaming. Protoplasm (hyalin cytoplasm) consists therefore of two phases: a visible dispersed phase and an optically empty medium.

Toxin-antitoxin Reactions on the Surface of Collodion Particles.—Jules Freund (from the Henry Phipps Institute, University of Pennsylvania). According to Bordet's theory the toxin-antitoxin reaction is an adsorption phenomenon controlled by the electrical charge of toxins and antitoxins. Bordet's theory is in harmony with all of the observations on toxin-antitoxin reactions, but it lacks direct evidence, for the electrical charge of toxins and antitoxins was not measured. It is probable that this could be accomplished if the reaction would be studied with a new method, that is, on the surface of particles instead of in solution. (The electrical charge of substances in highly dispersed state cannot be measured.) This report describes the reactions between toxins and antitoxin adsorbed on collodion particles.

Reaction Between Diphtheria Toxin and Antitoxin. Collodion particles treated with diphtheria toxin were flocculated by diphtheria antitoxic horse serum. When the collodion particles were treated with toxin that had been heated for two hours at 55° C., the flocculation by antitoxin was reduced considerably. Collodion particles treated with formalin-toxoid were also flocculated by antitoxin, and previous heating of the toxoid did not affect the flocculation phenomenon. Collodion particles treated with diphtheria toxin injected into the skin of guinea-pigs produced redness, edema, and superficial necrosis of the skin. The inflammation was prevented when antitoxin was injected simultaneously.

Neutralization of Tetanus Toxin Adsorbed Upon Collodion Particles by Antitoxin. Collodion particles treated with tetanus toxin were not flocculated by antitoxin. Indeed it was observed repeatedly that such particles could be more readily suspended in various dilutions of antitoxin than in saline. However, the presence of tetanus toxin upon the treated collodion particles and the neutralizing action of antitoxin was very clearly demonstrated by animal experiment. Tetanus toxin

adsorbed upon collodion particles is neutralized in five minutes even by a very high dilution of antitoxin (1 in 50,000). The question arises as to whether collodion particles treated in reversed order, first with antitoxic serum, and then with toxin, produced tetanus in mice. Collodion particles were treated (*a*) with antitoxic serum and then with toxin; (*b*) with normal horse serum and then with toxin; (*c*) with antitoxic serum, then with toxin and then with antitoxin again; (*d*) with toxin alone. Repeated experiments showed that the order of the toxicity of particles was as follows: $a > d > b > c$. In one out of five experiments *a* and *d* were equally toxic, but *a* was never less toxic than *d*. In other words, the antitoxin adsorbed on collodion particles failed to neutralize the toxin subsequently adsorbed, moreover collodion particles treated first with antitoxin and then with toxin were slightly but definitely more toxic than particles treated with toxin alone. In contrast to this, collodion particles treated first with normal horse serum and then with toxin were less toxic than those treated with toxin alone. This paradoxical phenomenon can be explained as follows: The protein film adsorbed on the particles from normal serum prevents the adsorption of toxin. Particles treated with antitoxin are also coated with protein but the antitoxin present in the film adsorbs toxin without being able to neutralize it. This is the first demonstration of a reaction between toxin and antitoxin with other than neutralization or flocculation. (See also *Proc. Soc. Exper. Biol. and Med.*, 1930, **28**, 65.)

The Retina as a Nervous Center.—RAGNAR GRANIT (from the Eldridge Reeves Johnson Foundation for Medical Physics, University of Pennsylvania). A short review of experiments published in the *American Journal of Physiology* for 1930, showing that the retina besides being a sense organ is also a "true nervous center" (Cajal), exhibiting typical synaptic reactions of decisive importance for an understanding of a number of phenomena of vision.

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